The influence of psychoactive drugs on brain self-stimulation behaviour

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I. Introduction

The present study deals with the influence of psychoactive drugs on self-stimulation behaviour in the rat. The term «self-stimulation» denotes the particular behaviour performed by the rat, in order to obtain electrical stimulation through chronically implanted electrodes in the brain. The discovery of self-stimulation by Olds and Milner (1954) occurred accidentally, but it was the start of numerous studies (see survey in: Brain stimulation reward; Wauquier and Rolls, 1976). In 1953, Jim Olds worked as a postdoctoral fellow together with the graduate student Peter Milner, who was experienced in surgical and electronic techniques, at McGill University in Canada. Olds was interested in the neurophysiology of learning. For this purpose, he used the rather new and still crude technique of chronically indwelling brain electrodes. These electrodes were aimed at the reticular formation, which was stimulated during learning at chosen points in a simple maze. During one of these experiments Olds observed that a rat did not run into an arm of the maze, but, rather, returned to the place where it had previously received brain stimulation. In the light of the experiments of Delgado et al. (1954), who showed the brain stimulation could elicit aversive reactions, it occurred to Olds that the rat apparently «liked» the stimulation. The behaviour could be evoked repeatedly and Olds together with Milner aimed to quantify this behaviour. For this purpose, the rat was placed into a Skinner box equipped with a lever, on which pressing evoked brain stimulation. To their surprise, the rat rapidly started to press the lever. Moreover, the rat continued for many hours and Olds, being afraid that this would not be repeatable, collected many meters of paper with cumulative recordings of the rat's activity. Although not certain, because histology could not been studied, it is likely that the electrode they had implanted went deeper than originally planned and arrived in the hypothalamic region. During subsequent weeks, many rats were implanted and it was confirmed that rats could be trained to press a lever for direct brain stimulation in septal and other regions.

Olds and Milner reported their original findings in 1954, and papers attractively entitled «Pleasure centres in the brain?» reached the public press. The phenomenon self-stimulation (term introduced by Brady, 1955) gained a world-wide popularity. The experiments of Delgado et al. (1954) on the one hand, and Olds and Milner (1954) on the other hand, suggested that «hell and heaven» were detected in brain.

During the years following the discovery, self-stimulation was shown in many species throughout the whole phylogenic scale, including Man.

Sem-Jacobsen and Torkildsen (1960) and Heath and Mickle (1960) (see survey by Sem-Jacobsen, 1976) demonstrated during stereotaxic surgery that electrical stimulation of particular brain areas in Man was experienced as pleasant. It is not without significance that a symposium dedicated to electrical brain-stimulation was entitled «The role of pleasure in behaviour» (Heath, 1964). This reflected the belief that pleasure could be caused directly in the brain by electrical current. Feibleman wrote: «The best interpretation seems to indicate that the stimulated animals are experiencing pleasure» (Feibleman, 1964). Together with the findings in humans by Delgado (see survey Delgado, 1976) the self-stimulation experiments contributed to the myth that control of human behaviour by stimulation through implanted electrodes was possible. Valenstein (1973) situated the experiments in their proper context by pointing out the limitations of evoked behaviour as opposed to the rich emotional variety of human behaviour and the restrictions imposed by ethical considerations.

Unfortunately, animals do not talk and describing self-stimulation by the rat in terms of pleasure sensations is an anthropomorphism. There are, however, many demonstrations of the fact that electrical stimulation of particular brain areas in the rat (and other species as well), is able to reinforce a variety of behaviours besides lever-pressing, such as maze learning and discrimination. Therefore, the electrical activation of certain neurons can be considered as rewarding. This means that reward and drive neurons are a special set of neurons, which contradicts, to a certain extent, the concept that reward is, rather, a property of certain unidentified systems, as formulated in the drive-reduction theory of Miller (1951, 1957) and Hull (1943) or the arousal theory of Hebb (1955) (see Olds, 1976).

«In terms of dramatic impact and the amount of theoretical speculation and experimentation generated, no single discovery in the field of brain-behavior interactions can rival the finding that animals could be highly motivated to stimulate certain areas of their own brain.» (Valenstein, 1973, p. 38). The Olds-and-Milner experiments resulted in a new emphasis on hedonistic explanations of behaviour, i.e. behaviour must be controlled by pleasant or unpleasant consequences of behaviour (Berlyne, 1973). The hedonistic principle is formulated in a famous sentence by Bentham (1789): «Nature has placed mankind under the governance of two sovereign masters, pain and pleasure.»

Whether a stimulus results in reward or aversion depends on the unconditioned reaction of the subject (Vossen, 1973), and manifests itself as respectively approach or withdrawal from the stimulus (see more details on this concept in publication by van der Staak, 1975). Brain stimulation directly elicits approach behaviour or withdrawal behaviour. Behaviour is steered by the reward (brain stimulation in «positive» areas) and the probability of the responses preceding reward is increased. Further, sensory signals become attached to the reward. A delicate functional balance between the two systems (mediating reward and aversion), must determine which behaviour is selected.

Whereas the arousal theory would maintain that drive-reduction is rewarding, i.e. source of reinforcement of responses closely following arousal reduction (e.g. Berlyne, 1960), important features of self-stimulation behaviour appeared inconsistent with this view. For instance, the lack of satiation, independence of a causal relationship with drives and the fact that brain stimulation aroused rather than reduced «arousal» in such areas as the lateral hypothalamus, made a reconsideration of certain motivational theories necessary. Even Miller (1961, 1963) a strong defender of the drive-reduction theory modified his view.

The neurophysiological bases of motivation became a major point of research. Mapping studies made it clear that lateral and far medial hypothalamic regions were rewarding areas whereas the areas in between were a mixture of rewarding and aversive. In the latter areas drive-effects could overlap and there is a certain relationship between self-stimulation and basic drives hunger, thirst, sex etc. (e.g. Hoebel, 1969). Many other experiments demonstrated that drives were not necessarily causally related to the phenomenon self-stimulation. Drives could, however, act as gates and co-determine final output.

A further question was whether self-stimulation could only be obtained in the hypothalamic areas. Anatomical mapping studies showed that the self-stimulation sustaining areas reached from olfactory-paleocortical areas of the telencephalon, through the ventral surface of the midbrain towards dorsal parts of the medulla (e.g. Olds and Olds, 1963).

Neurochemical mapping studies demonstrated that the reward system was localized from cellbodies in the medulla (noradrenergic) and in the ventral midbrain (dopaminergic) and followed the fibres to their terminal regions in the forebrain and cortex. There appeared, therefore, a marked overlapping between the catecholaminergic systems and the anatomical placements of the electrodes sustaining self-stimulation (German and Bowden, 1974). This formed the basis of the so-called «catecholaminergic theory» of self-stimulation (Dresse, 1966 and Crow, 1971). The study of the pharmacological influence on self-stimulation behaviour adopted a neurochemical approach.

The important question arose as to whether pharmacological substances applied systemically or intracerebrally affected the reward system, or rather affected a system common to instrumental learning in general. It could further be argued that the self-stimulation substrate is involved in all kinds of operant behaviour. It is, however, difficult to imagine that a reward system could operate without integration with other brain systems which modulate and/or determine final output.

The lesioning studies clearly demonstrated that behaviour does not reside at the tip of the electrode, but requires a coordinated functioning of various brain structures. A locus of self-stimulation as postulated by Olds and Olds (1965) could not be confirmed and Valenstein (1966) pointed out the interaction, plasticity and even redundancy of the brain structures. The experiments by Huston (1973) showed that rats extensively lesioned in forebrain structures continued to self-stimulate in the lateral hypothalamic region, provided that the behaviour was very simple and did not require spatial orientation.

These experiments emphasized the organization of reward at different levels of complexity of behaviour.
Reward is involved at different levels of CNS-organization: i.e. learning of motor skills, learning of behavioural sequences, learning of maps and objects (Olds, 1976). The research on self-stimulation behaviour and its manipulation by pharmacological substances may contribute «to understanding those parts of the behavior repertoire that are modifiable by training. To me these are the most important features of human behavior.» (Olds, 1976, p. 25).

II. Aims of the study

The present work deals with the influence of psychopharmacological substances on self-stimulation behaviour in rats with chronically implanted electrodes in the lateral hypothalamic region of the medial forebrain bundle.

A large number of papers, all dealing with the influence of psychoactive drugs on self-stimulation in rats, has been published since 1956. Because of considerable differences between these studies with respect to methodology, drug-description and drug-analyses, a comparative analysis and review of the results is difficult to achieve (Chapter III). The general methods applied in our experiments, are described in chapter IV.

Most studies on self-stimulation have been done on rats lever-pressing for brain-stimulation. From these studies, it is clear that the characteristics of the electrical stimulation parameters are very important factors in determining the rate of lever-pressing. However, studies in which the question as to how stimulus parameter combinations influence response rates is investigated systematically are rare.

Therefore, we examined the relationship between different combinations of stimulus parameters and lever-pressing rate. One of the hypotheses tested, was whether the quantity of charge contained in a stimulation, determined the number of lever-pressings. Further, because the assessment of drug-effects is partly dependent upon base-line responding, it was of interest to know whether systematic relationships exist between specific stimulus parameter combinations and rates of lever-pressing (Chapter V).

In a quantitative approach to a particular behaviour, drug-effects are defined as facilitatory or inhibitory, according to whether they increase or decrease base-line behaviour. In view of the fact that drugs can produce increase, decrease or both, we had to develop a standardized method which would make it possible to study the influence of a variety of psychoactive drugs. Different base-lines of responding were achieved by introducing different stimulus parameter combinations to the same rats, during the same session. The response rates obtained during control sessions, are determined by various factors, such as the stimulus parameter combinations, subjects, time of experiment, etc. An adequate analysis of the control data required a factorial approach. We therefore applied an analysis of variance to the control results obtained with a group of rats (Chapter VI.2.).

Next, the effects of various psychoactive drugs on rates of lever-pressing under adequate stimulus parameter combinations were studied.

The aim of the study was to construct profiles of lever-pressing, based upon these stimulus parameter combinations, which would enable us to differentiate groups of psychoactive drugs.
Special attention was paid to the problem of distinguishing between the effects of the drugs on the reinforcing properties of electrical stimulation (specific effects) and the effects of drugs on behavioural variables, such as general activity, which may affect rate of lever-pressing (unspecific effects). The effects of the drugs on lever-pressing behaviour were compared with the effects of the drugs on a number of other behavioural variables (Chapter VI.3.).
A large number of neuroleptics with well established clinical efficacy in the treatment of various psychiatric disorders, has been developed over the past 20 years. One of the characteristics of the neuroleptics is, that they cause a «specific» inhibition of operant behaviour. The inhibition of self-stimulation by neuroleptics has been used as evidence for a catecholaminergic involvement in self-stimulation. The particular problem studied in the present work, was to reveal the characteristics and nature of the neuroleptic-induced inhibition of self-stimulation, with particular emphasis on the rôle of the dopaminergic nigro-striatal system (Chapter VII).

III. The influence of psychoactive drugs on brain self-stimulation behaviour: a literature survey

127 papers, published between 1956 and 1974 and all dealing with the influence of psycho-active drugs on brain self-stimulation in rats, are reviewed here. The methods and results of these papers are summarized in tables and followed by critical remarks on methodology and description of the results. The interpretation of the effects of psycho-active drugs on self-stimulation is incorporated in the discussion of the experimental results (Chapters VI and VII).

1. MATERIAL COLLECTION

The classification of drugs used here is a compilation of different classifications made on pharmacological or chemical bases (e.g. Ehrart and Ruschig, 1972; Janssen, 1970; Janssen et al., 1965a) and should only be used as a guide-line.

1.1. Classification

I. Psycholeptics

1. Hypnotics or hypnosedatives
   - pentobarbital
   - phenobarbital

2. Neuroleptics

2.1. rauwolfia alkaloids
   - reserpine

2.2. benzoquinolizines
   - tetrabenazine

2.3. dimethylpropylphenothiazines
   - chlorpromazine
   - other phenothiazines

2.4. butyrophenones
   - haloperidol
   - other butyrophenones (spiroperidol, etc.)

2.5. diphenylbutylamines
   - pimozide
   - chlopimozide

3. Minor tranquillizers
   - chlordiazepoxide
   - diazepam
   - nitrazepam
   - meprobamate

II. Psychoanaleptics (psychic stimulants)

1. Vigilance stimulators
   - amphetamine (1)
2. Antidepressants
   - 2.1. Tricyclic antidepressants
     - imipramine
     - desipramine
     - amitriptyline
     - nortriptyline
   - 2.2. Mao-inhibitors
     - 2.2.1. hydrazides
       - iproniazid
     - 2.2.2. indolalkylamines
       - etryptamine
     - 2.2.3. cyclopropylamines
       - pargyline
     - 2.2.4. propargylamines
       - tranylcypromine
3. Other psychic stimulants
   - cocaine

III. Psychodysleptics

1. Related to indolalkylamines
   - LSD
2. Phenylethylamines
   - mescaline
3. Tetrahydrocannabinols
   - 9-tetrahydrocannabinol

IV. Cholinergics and anticholinergics

1. Cholinomimetics
   - 1.1. Cholinergic agonist
     - arecoline
   - 1.2. Acetylcholine-analogue
     - pilocarpine
   - 1.3. Anticholinesterase
     - neostigmine
     - physostigmine
   - 1.4. Ganglion stimulating agent
     - nicotine
2. Anticholinergics
   - 2.1. Muscarinic anti-cholinergics
     - atropine
     - scopolamine
     - dexetimide
   - 2.2. Tropine-derivative
     - benztropine

(1) dl-, d-, l-amphetamine and methamphetamine.

V. Narcotic analgesics
- fentanyl
- morphine
- piritramide

VI. Anticonvulsants
- diphenylhydantoin
- azetazolamide

VII. Drugs interfering with catecholamines
1. Blockade of NA-synthesis
   - α-methylparatyrosine
2. Dopamine-ß-hydroxylase inhibitors
   - diethyldithiocarbamate
   - disulfiram
   - Fla-63
3. Precursor
   - L-dopa
4. Direct receptor stimulation
   - apomorphine
5. NA-receptor blocking (1)
   5.1. α-blockers
      - phentolamine
      - phenoxybenzamine
   5.2. ß-blockers
      - propanolol

VIII. Drugs interfering with indolamines
1. Tryptamine and analogues
   - N,N-dimethyltryptamine
2. 5.-Hydroxytryptamine
3. Synthesis inhibitor
   - parachlorophenylalanine

1.2. Key to the tables

Compounds:	references in chronological order dose expressed in mg/kg body weight
Rte:	route of administration s.c.: subcutaneous; i.p.: intraperitoneal; or.: oral
Ti:	time of drug-administration

(1) Most of the neuroleptics described are considered to block DA-receptors (see Chapter VII section 6).

Brain structure: refers to the structure in which the electrode was implanted (all-or-none as demonstrated by histological examination);
abbreviations:

MFB:	medial forebrain bundle
VMH:	ventromedial hypothalamus
accumb.:	accumbens
amygd.:	amygdala
hypoth.:	hypothalamus
forebr.:	forebrain
midbr.:	midbrain
ant.:	anterior
dors.:	dorsal
dorsomed.:	dorso-medial
lat.:	lateral
post.:	posterior
ventr.:	ventral

Rats: number and sex
♀ female, ♂ male

Stimulus
- E electrode, monopolar (M) or bipolar (B)
- I intensity, in volts (V) or ampères (A)
- F frequency, number of cycles per second (℘) or pulses per second (pps)
- PW pulse width
- TD train duration = duration of the stimulation

Session: duration of the session, eventual subdivisions indicated

Procedure: refers to the schedule used
- CRF continuous reinforcement
- FR fixed ratio (ratio responses/stimulations)
- VI variable interval
- FI fixed interval

Results: the description is short, but as complete as possible
↗ denotes increase
↘ denotes decrease
special procedures are indicated when relevant to the data

1.3. Tables

The following tables are ranked according to the classification described in 1.1.

PENTOBARBITAL				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti.		N Sex	E.	I. μA	F.	P.W. msec.	T.D. msec.
Olds, J. et al. 1956	10. 15.	i.p.	-	a. septal area	6/8	B	1 to 1.5 V	60 ~	-	600
				b. post. VMH	6/8					
Olds, J. and Travis, R.P. 1960 a.	10.	i.p.	0	septal area	8	B	0, 10, 20, 30, 40, 50	60 ~	-	500
				ant. MFB	8					
				post. MFB	8					
				tegmentum	8					
b.	5.0 10. 15. 20.	i.p.	0	MFB	43	B	0, 10, 20, 30, 40, 50	60 ~	-	500
Mogenson, G.J. 1964	15.	i.p.	-10	basal part forebr.	10 ♂	B	30-75	60 ~	-	500
Stein, L. 1967	8.0									
Olds, M.E. 1972a	10.	i.p.	+30-45 min.	MFB	8 ♂ 5 ♂ 6 ♂ 7 ♂	B	T + 30-50 %	60 ~	-	500
PHENOBARBITAL										
Reid, L.D. et al. 1964 a.	15 30 45 60	or.	+ 5 min.	hypothalamus near MFB	12 ♂	B	30-100	60 ~	-	0-600
b.	45	or.	0	septal region	5 ♂	B	60-100	60 ~	-	-
c.	45	or.	+ 2 hrs	hypothalamus near MFB	4 ♂	B	26 to 160	60 ~	-	-
				septal area	2 ♂	B				

SESSION		RESULTS	REMARKS
Dur, min.	Proc.		
80	CRF	a. Slight depression at 10 mg/kg, not on second administration b. Little effect, even with marked motor depression	
6 x 8	CRF	a. Mapping: ↓12 %, ↑ 25 % 6 rats ↑, 3 ↓ ; 15· 0 effect Ineffective in tegmental and septal area	
6 x 8	CRF	b. Dose-response: wide-spread effect, ↑ and ↓, even at 20 mg/kg	Only data of the 30 µA-period
40		8 non-seizure rats non significant ↓ (17.2/min. → 13.4/min.) 2 rats with convulsive reactions: significant ↑ (from 9,9 to 20,2 and 5,7 to 15,4 lever-pressings)	
90	VI	No effect	No specifications
1) 30-45 2) 32 3) 80	CRF	1) Control SS 2) Injection chlordiazepoxide, amphetamine or scopolamine 3) Injection pentobarbital Small decrease in SS (65-88 % of control for 32 min.) CDP potentiated ↓ Initial ↓, later ↑ with amphetamine Scopolamine: same as with amphetamine	
5 min. periods at 1,2,3,4,5, 24,25,48, 49 hrs	CRF	. ↑ at 15 , 45 and 60 mg/kg highest at 4 hrs (respectively 122, 137 and 134 mean pressings of 3 subjects compared with control rates; at 30 mg/kg highest at 5 hrs (127 pressings)	% ratios of pressing rate under the drug to placebo rate
15 at 4 hrs and 28 hrs	CRF	. average ↑ : 50 % at 4 hrs, 38 % at 28 hrs	
3x5 separ by 1/2 hr		. three intensity levels· low (threshold: 26-44 uA), medium (45-84 µA), high (110-160 µA) ↑ at all intensities	

RESERPINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti. min.		N Sex	E	I µA	F	P.W. msec.	T.D msec.
Olds, J. et al. 1956	0.5 1.0			a. septal area b. medial hypothalamus c. amyg.	4 ♂ 3 ♂ 2 ♂	B	1-1.5 V	60 c/s	-	600
Olds, J. et al. 1957	1	i.p.	-60	septal region ventral region post. hypothalamus anter. tegmentum lat. part rhinenceph.		B	1 V (± 35 µA)	60 c/s		500
Stein, L. 1962 b	0.6 1.0	i.p.		hypothalamus midbr. tegmentum		B	0.25-0.50 mA	100 pps	0.2	150
Stein, L. 1964 a (and Stein L., 1967)	1.0 (5.0)	i.p.	3 hrs	hypothalamus anter. midbr. tegmentum	6 ♂	B		100 pps	0.2	150
Dresse, A. 1967	0.16 0.31 0.63 1.25	s.c.	-2 hrs	MFB (lat. hypothalamus)	8 ♂	B	< 160	50 c/s	-	500
Haley, T.J. et al. 1968	3.0	i.p.		7 ♀ dorsomed. hypothalamus 6 ♀ lat. hypothalamus 2 ♀ dorsomed. hypothalamus 1 ♀ lat. hypothalamus	15 ♀	B				
Gibson et al. 1970	0.3 0.5	i.p.		MFB post. hypothalamus	25 ♂	B	T: 5-14 V	60 c/s	-	150

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
80	CRF	a. ↓ to 75 % of normal (range 67-85 %) b. ↓ to 7-45 % of normal c. ↓ to 1-22 % of normal + Increase in sensitivity on successive adm	
60	CRF	-Septal region 0 effect (79-110 % of control) -Hypothalamus anter. tegmentum, lat. parts rhinenceph. pronounced ↓ -Posterior part brain 0-30 % of control, anterior less ↓ (max. 68 % of control)	
5 hrs	CRF thresh testing	Two lever situation one SS stepwise decrease in intensity, one (reset lever) resets current to the top set (6 4 mA) 1.0 mg/kg elevation threshold after 45 min., pausing 2 hrs, finally ↓↓, 3 days later abnormally high 0.6 similar effect Reversal by dl-amphetamine (0 25-1.0)	
Test at 1, 2, 24 hrs	CRF	Reserpine + at 0, 1, 3 or 24 hrs d-amphetamine 1 mg/kg.effects of amphetamine diminished or shortened at all intervals. Sharp↓ at 1 2, 3 hrs, slight↓ at 24 hrs 5 mg/kg dismished effect amphetamine 1 example of eight weekly inj. 1.0 mg/kg Reserpine inhibition more rapid	
8		Max.↓ 2-8 hrs. With 0.16· 0 effect at 5 hrs 1.25 sign. to 32-48 hrs 5.0 . 3 rats inhib. up to 72 hrs ED_{50}: 2 hrs. 0.27 (.16-.41) 5 hrs· 0.31 (.19-.49) 8 hrs. 0.33 (.22- 49) 24 hrs 0 60 (.35-1.0) 32 hrs 0.87 (62-1.2) 48 hrs >1.25	
60	CRF	Daily sessions for approx. 40 days 5 0 mg/kg (3 0 mg/kg effect similar) high sedation at 24 hrs, not fully recovered for 3 days 50 % of control (mean for 3-10 days) Recovery only to 78 % of control (10-28 days)	
day?		Voltage difference betw thresholds following administration of a drug and the control-threshold taken as the effect of the drug. Δ threshold (n rats) +1 1 V +2.2 V +3.3 V 0.3 mg/kg 12 8 2 0.5 mg/kg 0 0 3	% of control NA 5HT 95 80 70 70

TETRABENAZINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	TI min		N Sex	E	I µA	F	P W msec	T D msec
Poschel, B P H., Ninteman, F W 1963	2	i p.		lat hypothalamus	3 ♂	M	20-30	60 %	-	400
Stein, L. 1967										
Dresse A 1967	0 31 1.25 5.00	s c	-120	MFB (lat hypothalamus)	8 ♂	B	< 160	50 ♀♂	-	500
Haley T J et al. 1968	40	i p		2 ♀ MFB 1 ♀ dorsomed hypothalamus 1 ♀ lat hypothalamus	4 ♀	B				
Olds, M E 1972 a	a 2.0	i p	+77	MFB	7 ♂					
	b 2 0	i p	+62-77	MFB	7 ♂	B	30-50 % above T	60 ♀♂		500
Olds, M E., Ito, M 1973	4	i p	+30	post lat hypothalamus	44 ♂	B	5 V	80 pps	0 3	250

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
7-8 hrs	CRF	- Complete ↓ for 3.5 hrs. - Pretreatment parnate (1 mg/kg) SS ↗.	
		Brief stimulation with 2.0 mg/kg tetrabenazine, 17 hrs after pargyline 50.0 mg/kg	One example.
8 periods 2, 5, 8 hrs	CRF	0.31 mg/kg almost ineffective 1.25· complete at 2 hr, recovery to 50 % at 5 hrs 5.00 complete at 2 and 5 hrs, recovery 50 % at 8 hrs ED_{50} at 2 hrs 0.63 (.32-1.23) 5 hrs 1.48 (.94-2.34)	
60	CRF	Sedation for 24 hrs, within control range 2 days post-administration	Daily session for > 33 days.
1. 45 2. 32 3. 80	CRF	1 SS - no drug 2 SS - injection saline 3. SS - injection tetrabenazine Effect ↓ at 8 min. 32 %, at 16 min.: 83 %, at 24 min. 94 % → 100 %	
1 30-45 2. 32 3. 80		1. SS - no drug 2. SS - injection amphetamine (2.0 mg/kg), scopolamine (0.5 mg/kg) or chlordiazepoxide (5.0 mg/kg) 3 SS - injection tetrabenazine Amphet protection↔tetrab., throughout 80 min Scopol delay depression at 8, 16 and 24 min. Chlordiaz delay (16-24 min) - did not potentiate.	
30+ 30+ 45	CRF	1° period (30 min) SS 2° period (30 min) SS after injection tetrabenazine ↓ at 15-30 min after injection 3° period (45 min) injection amphetamine (2 mg/kg). SS reinstated, 5-15 min after injection	SS correlated with neuronal activity.

CHLORPROMAZINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETERS				
REFERENCE	Dose mg/kg	Rte	Ti. min.		N Sex	E	I µA	F	P.W msec.	T.D. msec.
Olds, J. et al. 1956	2.5			Middle hypothalamus Septal area Amygd. area	? 6 2	B	1 to 1.5 V	60 ♂	-	600
Miller, N.E. 1957	4			Hypothalamus	?					
Olds, J. et al. 1957 Olds, J. 1958	a. 2.5	i.p.	-10	Ventral poster. hyp. Lat. parts rhinencph.	17	B	1 V (± 65 µA)	60 ♂	-	500
	b. 2	i.p.		Poster. middle anter. hypothalamus Anterior preoptic Septal region Anterior septal	31	B	0-55			
Olds, J. 1959 Olds, J. et al. 1957	2.0	i.p.		Diff. parts hypoth.		B	0-10 20-30 40-50	60 ♂	-	500
Olds, J., Travis, R. P. 1959 and 1960	a. 2.0	i.p.		Post. to anter. hyp. area Septal area MFB	6/8 per group 4x8-9	B	0-10 20-30 40-50	60 ♂	-	500
	b. 0.5 1.0 1.5 2.0	i.p.								
Stein, L., Ray, O.S. 1960	1.5	i.p.	+1 - 1.5 hrs	Poster. hyp. Midbr. tegmentum	6 ♂	B	0 to 7.5 mA	50 pps	50 µsec. interval 200 usec.	250
a. Stein, L. and Seifter, J. 1961 b. Stein, L. 1962 a, b, 1967	3.0	i.p.	-	Poster. hypothalamus Midbr. tegmentum		B	100-250	100 pps	0.2	150
Olds, M.E. and Olds, J. 1964	1.0 1.5 2.0	i p	+32	lat. hypothalamus tegmentum	5 ♂ 6 ♂	2xB	40-60	60 %	-	250

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
80	CRF	Hyp. ↓ 8-11 % of normal Sept. ↓ 0-38 % of normal (0-77 % range) Amygd. ↓ 1-17 % of normal	
105	CRF	On one lever pressing: ↓ to ± 35 % after 1/2 hour	Two levers placed diagonally: one to turn the stimulation on, one lever to turn the stimulation off. Experiment by Kirschner. No further details.
60	CRF	a. Mapping effect: - medial area: 12 → 83 % of control - lateral area 0 → 92 % of control - septal area 8 → 88 % of control Greatest effect posterior part	Refers to experiments 1956.
6x8	CRF	b. Strong ↓ ventral posterior hypothalamus, forwards in hypothalamus: slight ↓ to 0, mild ↓ in septal and sub-septal regions.	Increase μA in steps of 5 to 10 each 8 min period. Mapping effect in 6 cross sections with 2-9 points tested in rectangle 1,5 mm above the base of the brain, 1,5 mm lateral.
6x8	CRF	↓ almost complete 5 consecutive days of injection ↓ (0-40 %) of control in all points tested	Almost no effect on escape
6x8	CRF	a. Mapping effect varied according to SS rate: higher rate SS most inhibited b. Dose-response 2 0 almost complete ↓, lower doses slight ↓ (50 % between 1,5 and 2,0 mg/kg)	See Olds, J. et al., 1957
		Threshold raised. Onset. 15 min.	Two lever situation one lever (stimulation lever) SS and stepwise decrease in intensity, second lever (reset lever) resets current to top value (7,5 mA).
		a. At threshold current: antagonism of ↑ by d-methamphetamine (0,25 mg/kg) b. Same results - mention that 1,5 mg/kg of chlorpromazine produces a substantial prolongation of methamph. (1,25 mg/kg)	Cumul. record of one rat
16x8		1. One electrode in LH, one in tegmentum (escape) Each period of 8 min consisted of. 1. 2 min SS on LH 2 2 min SS on T 3. 2 min escape LH 4. 2 min escape T Analysis of 16 x 2 min periods SS in LH (and comparison escape) SS Escape 1.0 mg/kg 0 0 1.5 mg/kg ++ 0 2.0 mg/kg +++ ++(+) Effects lasted the total 96 min post-injection.	

CHLORPROMAZINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti. min.		N Sex	E	I μA	F	P W. msec.	T D. msec.
Dresse, A. 1966 and 1967	a. 0.31 1.25 5.00	s.c.	-2 hrs	MFB (lat.hyp.)	6 ♂	B	-T T +T	50 ♀	-	500
	b. 6.4	s.c.	0 hr	MFB	6 ♂		T+			
Stark, P. et al. 1969	0.5 2.0 5.0	i.p.	-15	Septal area Anter. mid. hypoth. Poster. hyp. Midbr. tegmentum	>3 ♂ >3 ♂ >3 ♂ >3 ♂	B	T=15 T=15 T=20 T=20	60 ♀	-	250
Olds, M.E. 1972a	a. 2.0	i.p.	+77	MFB	7 ♂					
	b. 2.0	i.p.	+62 -77	MFB	7 ♂	B	30-50 % above T	60 ♀	-	500
Ritter, S. and Stein, L. 1973	1.5 3.0 6.0	i p	0	locus coeruleus	4 ♂	B	8-40	100 pps mono-phasic	0.2	120

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
24 (3x8) 8 periods each hour 1-8 hrs	CRF CRF	a. $\bar{R}$/8 min solvent· 361 1.25 mg/kg· 318 0.31 mg/kg 331 5.0 mg/kg· 18 ED_{50} inhibition.2.0 (1.27-3.16) mg/kg b. Complete inhibition reached at 2-5-6 hrs. Recovery at 7 hrs 50 %. ± 80 % at 8 hrs.	
10+4x10		Total effect gradual inhibition at increasing doses. Post.hypothalamus animals less affected by low dose (0.5 mg/kg).	Ten minute periods at T (threshold intensity) T-1, T+1, T+2 (± 1 = 5 μA).
1. 45 2. 32 3. 80 1. 30-45 2. 32 3. 80	CRF	1. SS - no drug 2. SS - injection saline 3. SS - injection tetrabenazine 1' 8 min 49 % ↓ 2' 8 min: 96 % No recovery for 80 min 1. SS - no drug 2 SS - injection amphetamine (2.0 mg/kg), scopolamine (0.5 mg/kg) or chlordiazepoxide (5.0 mg/kg) 3. SS - injection tetrabenazine - amphetamine (2.0 mg/kg) protects fully 60 % at 24 min, 100 % at 48 min - scopolamine (0.5 mg/kg) protects fully throughout 80 min - chlordiazepoxide (5.0 mg/kg) sign. protection only at 24 min	
120	CRF	↓ % of saline. 1.5 mg/kg. ± 75 % 3.0 mg/kg ± 30 % 6.0 mg/kg ± 10 %	Fig. representation

HALOPERIDOL				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCES	Dose mg/kg	Rte	Ti hr		N Sex	E	I	F	P.W. msec	T.D. msec
Dresse, A. 1966 and 1967	0.01 0.04 0.16	s.c.	-2	MFB (lat. hypothalamus)	8 ♂ per dose	B	3 V 3.5 V 4 V	50 ↯	-	500
Kadziolawa, K. 1973 and 1974	0.05 0.15 0.25			post. lat. hypothalamus	♂	B	15-70	50 ↯	-	400
Lippa, A.S. et al. 1973	0.01	intra ven- tr.		post. hypothalamus	4 ♂	B		200 pps	0.2	300
SPIROPERIDOL										
Dresse, A. 1966 and 1967	0.005 0.02 0.08	s.c.	-2	MFB (lat. hypothalamus)	8 ♂ per dose	B	3 V 3.5 V 4 V	50 ↯	-	500
Rolls, E.T. et al. 1974 a, b	0.02 0.05 0.1 0.25	i.p.		-ventral tegmentum area -hippocampus -anter. hypothalamus -septal area -nucl. accumb.	7 ♂	SM	1.5 x T	200 pps	0.1	300

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
1) 3x8 2) 9x8	CRF CRF	S 478 ± 38 ED_{50} 0 052 0.01 410 ± 41 0.04 331 ± 53 Limits 0.034 - 0.080 0.16 30 ± 15 Onset and duration of 0.16 mg/kg: < 1/2 h < 7 h Peak depression at 1 h.	1) 1° period infraliminar intensity (50 R/8 min). 2° and 3° period increase 0 5 V. 2) Duration activity 8-min periods 1/2 h and at each hr up to 8 hr.
4 cycles of 2400 R		1) 0.05 mg/kg ↓ 25 % 0 15 mg/kg ↓ 0.25 mg/kg complete blockade for 3-4 h. 2) Increase after Dopa, attenuated or prevented by 0.05 mg/kg of haloperidol.	
		% of mean SS rate for 3 pre-drug days 46 %.	No motor impairments.
1) 3x8 2) 9x8	CRF CRF	S 431 ± 22 ED_{50} 0.01 0 005 426 ± 34 0.02 83 ± 15 0.08 1 ± 0.7 Onset Duration Peak depression <1/2 h >8 h 3 h	1) 1° period infraliminar intensity (50 R/8 min). 2° and 3° period, increase 0, 5 V 2) Duration activity 8-min periods 1/2 hr and at each hr up to 8 hr.
3 + 5 x 5		- 3 min SS in anter. hypothalamus - thereafter 5 min on each electrode, with 1 min time-out, - Dose-related decrease at different sites SS rate % of placebo (± values) Spiroperidol mg/kg 0.02 0.05 0.1 0.25 nucl. accumb. 62 40 15 - septal area 70 15 5 - hippocampus 55 5 15 - anter hypothalamus 95 60 15 - lat. hypothalamus 70 50 - 5 ventral tegmentum area 100 70 - -	Fig. - SS decreased relative to the base-line. - Attenuation SS > feeding > drinking. - Similar ↓ when bar-pressing is the required response.

ACEPERONE					RATS	STIMULUS PARAMETER				
REFERENCES	Dose mg/kg	Rte	T1 hr	BRAIN STRUCTURE	N Sex	E	I	F	P W msec	T D msec
Dresse A 1966 and 1967	5 0 20 80	s c	-2	MFB (lat hypothalamus)	8 ♂ per dose	B	3 V 3 5 V 4 V	50 ↯	-	500
BENPERIDOL										
Dresse A 1966 and 1967	0 005 0 02 0 08	s c	2	MFB (lat hypothalamus)	8 ♂ per dose	B	3 V 3 5 V 4 V	50 ↯		500
DROPERIDOL										
Dresse A 1966 and 1967	0 01 0 04 0 16	s c	-2	MFB (lat hypothalamus)	8 ♂ per dose	B	3 V 3 5 V 4 V	50 ↯		500
TRIPERIDOL										
Dresse A 1966 and 1967	0 01 0 04 0 16	s c	-2	MFB (lat hypothalamus)	8 ♂ per dose	B	3 V 3 5 V 4 V	50 ↯		500

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
1) 3x8	CRF	S 408 ± 27 ED_{50} 42 5.0 348 ± 50 10 318 ± 58 Limits 21.1 - 83.6 20 121 ± 56 Peak depression	1) 1° period infraliminar intensity (50 R/8 min). 2° and 3° period increase 0 5V
2) 9x8	CRF		2) Duration activity 8-min periods 1/2 h and at each hr up to 8 hr
1) 3 x 8	CRF	S 515 ± 25 ED_{50} 0 03 0 005 499 ± 29 0.02 377 ± 55 Limits 0 020 - 0.045 0.08 13 ± 13 Onset Duration Peak depression < 1/2 h > 8 h 2-3 h	1) 1° period infraliminar intensity (50 R/8 min). 2° and 3° period increase 0 5V
2) 9 x 8	CRF		2) Duration activity 8-min periods 1/2 hr and at each hr up to 8 hr.
1) 3 x 8	CRF	S 473 ± 36 ED_{50} 0.053 0.01 446 ± 33 0.04 315 ± 53 Limits 0 035 - 0.081 0.08 90 ± 28 Onset Duration Peak depression < 1/2 h < 6 h 1/2 h	1) 1° period infraliminar intensity (50 R/8 min) 2° and 3° period increase 0 5V
2) 9 x 8	CRF		2) Duration activity 8-min periods 1/2 hr and at each hr up to 8 hr
1) 3x8	CRF	S 510 ± 37 ED_{50} 0.035 0 01 461 ± 38 0.04 280 ± 56 Limits 0 022-0.056 0 16 61 ± 28 Onset Duration Peak depression < 1/2 h >8 h 2 h	1) 1° period infraliminar intensity (50 R/8 min). 2° and 3° period increase 0.5V
2) 9x8	CRF		2) Duration activity 8-min periods 1/2 h and at each hr up to 8 hr.

PIMOZIDE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti. hours		N Sex	E.	I. µA	F.	P.W. msec.	T.D msec.
Janssen et al. 1968	0.16 0.31 0.63 1.25	s c.	-2	MFB	5 ♂	B	80 64 48 32	50 %	-	500
Liebman, J.M. and Butcher, L L. 1973	0.35 0.50	i. p.	-3	1 lat. hypothalamus 1 mesenceph. gray	16 ♂ 10 ♂	2xB	15-40	60 %	-	100
Ritter, S and Stein, L 1973	0 5 1.0	s c	-4	locus coeruleus and MFB	3 ♂	2xB	8-40	100 pps mono phasic	0.2	150
Liebman, J.M. and Butcher, L L. 1974	0.35 0.50	i p	-3	1 lat hypothalamus 1 substantia nigra	16 ♂	2xB	-	60 %	-	200 every 2 sec.

SESSION		RESULTS	REMARKS
Dur min	Proc		
4 x 8 at 2 5 8, 32 and 48 hr after inj	CRF	Control mean interval between two successive responses for the 5 rats 0 8, 1 5 1 7 2 1 and 2 2 Pimoside - ↓ 50 % and ↓ 90 % 0 16 mg/kg 0 63 mg/kg (rat 2 and 3) 0 31 1 25 (rat 1 and 5) 0 63 0 63 (rat 4) Estimated s c dose which gives 50 % ↓ 0 2 mg/kg 90 % ↓ 0 6 mg/kg Duration highest ↓ at 5 and 8 hrs after injection	Analysis of the effects at the two most stable of the four 8 min periods
30+10 15	CRF	First period of session intensity yielding 50 75 % of maximal rate second period double current Marked ↓ Effect of 0 35 mg/kg less severe and greater individual variability Doubling current no alteration of ↓ with 0 5 mg/kg at 0 35 mg/kg ƒ to baseline	No sedation or obvious motor disabilities
2x60	CRF	MFB 0 5 mg/kg 100 4 % ± 5 4 1 0 mg/kg 69 8 % ± 3 2 Locus coeruleus 0 5 mg/kg 92 5 % ± 6 8 1 0 mg/kg 89 7 % ± 6 1	Pimoside injected s c as an aqueous suspension - 1 hr on MFB 1 hr on locus coeruleus
2x14		0 35 mg/kg ↓ SN 0 50 mg/kg ↓SN ↓HL ↓SN > ↓HL	Rate free test of SS every 2 sec 1 S in one of the sides of the cage every 2 3 min sides switched

CHLORDIAZEPOXIDE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti min		N Sex	E	I µA	F	P W msec	T D msec
Olds M E 1966	5 0	i p	-5	post hypothalamus anter hypothalamus	10 ♂ 4 ♂	M	50(rms)	60 c/s	-	250
Gandelman, R Trowill, J 1968	15.	i p	20	lat hypothalamus	4x4 ♂	2xM	35-120(rms)	60 c/s		500
Stark P et al 1969	0 5 2.0 5 0	i p	-15	septal area antero midd hypothalamus post hypothalamus midbr tegmentum	>3 ♂ >3 ♂ >3 ♂ >3 ♂	B	T - 15 T = 15 T - 20 T = 20	60 c/s	-	250
Pankseepp, J et al. 1970	15	i p	-15	hypoth area	a 15 ♂ b 15 ♂ c 15 ♂	B	25 70 µA T+5-10 µA T+-x 5 µA	60 c/s	-	500
Olds M E 1970	5 0	i p	+30	post lat hypothalamus	14 ♂	B	-	60 c/s	-	250
Domino E F , Olds M E 1972 Olds M E 1972 b	2 5 5 0 10 20 40	i.p	+30 -45	lat post hypothalamus	17 ♂	B	40-60	60 c/s		250

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
6 x 8	CRF	Mean change: 153 % (↑) (range: 125-276) Mean change 30.2 % (↓) (range. 18.0-62.4) Max. effect 24 min after injection, lasting the total session	6 electrodes in same region each tested for 8 min.
30	CRF	No difference to reach criterion between treated and non-treated animals (551 min. vs 575 min.) Resistance to extinction in group treated during acquisition and extinction: mean 124 R compared with 30.5 to 55.2 extinction responses in other groups	Before acquisition test 3 consecutive days of injection. Criterion time in min. to reach 1800 responses Groups treated (D) during acquisition and extinction D-D ND-D D-ND ND-ND
10+4x10 at T, T-1, T+1, T+2	CRF	T = threshold current + or - 5 µA (T-1, T, T+1, T+2) at random in session Lowering threshold in post. hypoth. and midbr tegmentum Decrease high rates of responding at supra -threshold intensities	
60 10 + 20 5+7x5	CRF	a. Group drug-high ↑ in 10 rats Group not drug-high: ↓ in 6 rats b On threshold testing (decreasing steps of 2 µA) high current levels ↓ lower (4 steps) ↑ in group not drug high Group drug high ↑ at all supra-threshold current levels c Rate-intensity (current increase 5 µA every 5 min.) Isomorphic curves as b.	CDP increased self-stimulation rates primarily from electrodes that also yielded reliable escape
30+80	CRF	Control rate 18 min. 479 (range < 150 >1050). ↑ all rate, in many instances lasting the 80 min. session, sign. at 8, 16, 24 and 32 min. No sign. effect on extinction	CDP facilitated SS especially in high rate self-stimulators
30+80	CRF	Various groups responses < 100/8 min (n=3), 100-350/8 min. (n=6), 350-750/8 min. (n=5), 750-1200/8 min (n=3) Doses 2 5, 5 0: ↑ 80 %, 24 min after injection. 10 and 20 mg/kg ↓ , 24 min. after injection Low responders: slight ↑ , rates at 32 and 56 min. equal to control. Moderate responders: ↑ , peak effect at 24 min., lasting 48 min. High responders ↑↑ , peak at 24 min. and lasting the 80 minute session.	Marked individual variation Effect only with 5.0 mg/kg CDP depressed responding in non-self-stimulators or in naive animals

CHLORDIAZEPOXIDE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETERS				
REFERENCES	Dose mg/kg	Rte	Ti. min		N Sex	E.	I. µA	F.	P.W msec	T.D. msec
Olds, M E. 1972 a Olds, M.E. 1972 b	5.0	i.p	+30 -45	MFB	32 ♂	B	T +30-50 %	60 ~	-	500
DIAZEPAM										
Olds, M.E. 1966	5	i.p.	-5	post. hypothalamus	10 ♂	M (6)	50	60 ~	-	250
				ant. hypothalamus	6 ♂	M (6)				
MEPROBAMATE										
Olds, J. 1959	80	i p.		anter. forebrain MFB. post. middle hypothalamus		B	10 20 30 40 50	60 ~	-	
Olds, J. and Travis, R P. 1959	a 80	i.p.	0 ?	a. septal region. hypoth. tegmental region	21 ♂	B	10 20 30 40 50	60 ~	-	
	b. 80 100 120 160	i.p.	0 ?	b. MFB	4 ♀ >6 ♂	B				
Olds, J. and Travis, R P. 1960	a. 80	i.p.	0 ?	a. septal region anter. MFB post. MFB tegmentum	6/8 per region	B	10 20 30 40 50	60 ~	-	500
	b. 80 100 120 160			b. MFB	>6 per dose					
Olds, M.E., Olds, J. 1964	40 60 80	i.p.	+32	lat. hypothalamus (LH) tegmentum (T)	7 ♂	2xB	40-60	60 ~	-	250
	60 80 100	i.p.	+32	anter and post. hypothalamus	3 ♂	2xB				
Weinreich, D. and Clark, C.D. 1970	50	i.p.		MFB	4-10 ♂	B	50-100	175-250 pps	0.1	500

SESSION		RESULTS	REMARKS
Dur. min.	Proc		
1) 30-45 2) 32 3) 80	CRF	1) Control SS 2) Inj. CDP and SS 3) Inj depressant drug CDP: ↑, peak at 24 min., lasting 48 min. No protection against tetrabenazine (2.0 mg/kg) delaying action lasting 16-24 min. Only slight protection against chlorpromazine (2 5 mg/kg), sign. at 24 min No effect against physostigmine (0 1 mg/kg) Potentiat.of the depressant effects of pentobarbital (10 mg/kg)	
6 x 8	CRF	Mean % change: 163 (± 47) Mean % change: 107 (± 56)	Each rat had 6 electrodes in each structure, tested for 8 min.
1+5 x 8	CRF	a. ↑ in ambivalent region: 0 or slight ↓ in MFB b. points tested in hypothalamus and adjacent regions. ↗ in regions of ambivalence (17 points)	2 examples
6 x 8	CRF	a. Mapping ↗ in ambivalent region Mild ↘ in other regions b. No general ↓ (↑ and ↓) Median values 80-90 % of control with 80-120 mg/kg, ± 50 % at 160 mg/kg	b. Data at 30 µA
6 x 8	CRF	a. Mapping: - sign ↑ in 39 % of the cases and 32 % ↓ - tegmental area: all (-1) ↑ - septal region all (-1) ↓ - hypothalamus most of the rats 0 effect b. Dose-response (median values) slight ↑ with 80 mg/kg slight ↓ with 100 and 120 mg/kg ↓ 50 % with 160 mg/kg	
16 x 8 16 x 8		1. One electrode in LH, one in T (escape). Each period of 8 min consisted of: 1. 2 min. SS on LH 2. " SS on T 3. " escape LH 4. " escape T Analysis on 2 min periods: - no pronounced dose-relationship - effect of 100 mg/kg % of control (median-range) SS / Escape 0-48': 84 (28-116) / 47 (0-57) 48-96': 105 (91-274) / 28 (11-49) 2. Both electrodes in hypothalamus 2 min SS - 2 min time out ↓ whole session with high doses	
10 ?	CRF	± 18 % ↑ (tested at peak effect 30, 60 or 120 min, but not defined)	

AMPHETAMINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Tl. min.		N Sex	E	I. µA	F.	P W. msec.	T D msec.
Olds, J. 1959										
methamphetamine	3.0	i.p.		anter. forebrain; MFB; post. middle hypothalamus		B	10, 20, 30, 40, 50	60 $\frac{c}{s}$		
amphetamine	3.0	i.p.								
Stein, L. and Rav O.S. 1960										
dl-amphetamine	0.75	i.p.	+60 -90	post. hypothalamus midbr tegmentum	6 ♂	B	0-7.5 mA	50 pps	50 µsec (200 µsec interval)	250
Stein, L., Seifter, J. 1961										
d-methamphetamine	0.25	i.p.	-	post. hypothalamus midbr. tegmentum	♂	B	100-250	100 pps	0.2	150
Stein, L. 1962 a										
d-methamphetamine	0.25	i.p.	$\pm$ 15	post. hypothalamus midbr. tegmentum	12 ♂ in total	B	100-250	100 pps	0.2	150
	0.50									
d-amphetamine	0.50									
Stein, L. 1962 b										
methamphetamine	1.5	i.p.		post. hypothalamus midbr. tegmentum lat. hypothalamus	♂	B	0-6.4 mA	100 pps	0.2	150
d-amphetamine	0.5	i.p.								
	0.75									
	1.0									
	2.0									
Olds, M.E. and Olds, J. 1964										
amphetamine	2	i.p.	+ 32	lat. hypothalamus tegmentum	5 ♂	2xB	40-60	60 $\frac{c}{s}$	-	250
	3									

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
3-5x8	CRF	↑ middle hypoth. ('ambivalent' region) ↑ MFB (on 30, 40 and 50 μA)	Map of SS in different hypothalamic regions. Greatest effects in area of overlap of sympathetic and parasympathetic points (= dorsal post. hypothalamus, ventral middle hypothalamus and the dorsal anter.)
210	thresh. testing	Amphet. lower threshold, onset: 5 min. Resetting at ± 3.4 mA (< than preferred int. = 25-50 mA)	Two lever situation. one SS with stepwise decrease in intensity, one (reset lever) resets current to the top set.
>120	CRF ? thresh. current	↑ onset, 15 min. Potentiation by imipramine (5.15 mg/kg) Antagonism by chlorpromazine (3 mg/kg)	1 cumul. record of representative rat
>120	CRF ? thresh. current	Sharp ↑ ; current off: no effect Potentiation by imipramine (< 20 mg/kg), amitriptyline (<30 mg/kg), iproniazid (100 mg/kg), etryptamine (2.5 mg/kg), chlorpromazine (1.5 mg/kg), cocaine (5.0 mg/kg), antihistamines: diphenhydramine (3.5, 10 mg/kg), chloroten (3.5, 10 mg/kg) Antagonism by chlorpromazine (> 1.5 mg/kg)	Examples of cumulative records
300	CRF ? thresh. testing	Lat. hypothalamus: lowering threshold and less pausing.	Two lever situation (see Stein and Ray, 1960). Same results as Stein 1962a.
16x8		One electrode in LH and one in tegmentum (escape). Each period of 8 min consisted of: 1. 2 min SS on LH 2. 2 min SS on T 3. 2 min escape LH 4. 2 min escape T Analysis of 16 x 2 min periods SS in LH "Uncertain effects on the very rapid approach behaviors".	Augm. effects on the slower escape behaviours.

AMPHETAMINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	TI min.		N Sex	E.	I. µA	F.	P W msec	T.D. msec
Stein, L 1964a 1967										
methamphetamine	0.5	i.p.	+15	areas of hypothalamus and anter. midbrain tegmentum	10 ♂	B	T int.	100 pps	0.2	150
d-amphetamine	0.25 0.50 1.00	i.p.	+15							
l- & d-amphetamine	0.25 0.50 1.00	i.p.	+15							
Wanner, H.U., Battig, K. 1966	1 2	i.p.	- 1	lat hypothalamus (MFB)	8	M	40-120	200 pps	2	500
Mogenson, G J 1968										
amphetamine	1.0	i p	-10	lat. hypothalamus	a 8 b. 15	B	28-50(rms)	60 ♀	-	a.200 b.1200
Stark, P et al 1969										
d-amphetamine	0 3 1 0 3.0	i p.	-15	a) septal area b) anter. mid. hypothalamus c) post. hypothalamus d) midbr. tegmentum	>3 >3 >3 >3	B	T = 15 T = 15 T = 20 T = 20	60 ♀	-	250
Crow T.J. 1969										
methamphetamine	0 25 0.4		-	ventral midbr. tegmentum	7 ♂	B	T	100 ♀	0 5	400
Olds, M E. 1970										
d-amphetamine	2 0	i p	+32	post. lat hypothalamus	>13 ♂	B		60 ♀	-	250
Olds, M E. 1972 a Olds, M.E. 1972 b										
d-amphetamine	2.0	i p.	+30 à 45	MFB	8 ♂ groups 6-8 ♂	B	30-50 % above T	60 ♀	-	500

SESSION		RESULTS	REMARKS
Dur. min.	Proc		
	CRF and VI	Effect of interaction d-amphet.. (1.0 mg/kg) and reserpine (1.0 mg/kg). 6 rats highest ↓ at 3 hrs, recovery 20-40 % of control at 24 hrs. Eight weekly injections reduce effect of amphetamine (> third weekly injection).	Review of results of previous papers. Examples are given of 10 rats (2 out of previous papers).
12 x 2.5	CRF	Testing on high (H) and low (L) current. Number of S per min % NaCl Amph. (1) Amph. (2) H: 82.2 91.4 82.1 L. 44.8 82.4 72.7	Sequences of 2.5 min on high, followed by 2.5 min on low current.
30	CRF	a. ↑ (control ± 2500 R - drug. ± 3500 R) water intake in 12/15 rats b. Concurr. drinking and SS 668 R/ 30 min → 858 R/30 min	
10+4x10	CRF	↑ low rates, ↓ high rates (T+1 and T+2). Post. hypothalamus rats least sensitive to amphetamine.	Periods of 10 min at T (= threshold current), T-1 (1=5μA), T+1, T+2
1 hr periods	CRF	Sign. ↑ at reduced current levels No diminution when pretreated with 0.61 mg/kg of methysergide bimaleate (1 hr or 3 hr) α-methyl-paratyrosine + amphetamine (0.4 mg/kg) at 1 hr and at 12 hr interval. Up to 6 hrs substantial ↓ in the 2 hrs after each dose Thereafter gradual recovery (till 60 h).	T not defined Repeated injection of 0.4 mg/kg methamphetamine
80	CRF	Variable ↑ dependent on resp. rate a largest ↑ for low resp (R 150-300/ 8 min), b no SS (< 150 R/8 min) ↑ lasting 80 min , c, moder SS (>350, < 750 R/8 min.) sign ↑ but indiv variability high SS ↓ , others ↑ . d resistance to extinction	
a) 30-45 b) 32 c) 80	CRF	a) SS - no drug b) injection amphetamine c) injection saline, tetrabenazine (2.0 mg/kg), chlorpromazine (2.5 mg/kg), physostigmine (0.1 mg/kg) or pentobarbital (10 mg/kg) Amphetamine injection slight ↑ , short duration	High SS

AMPHETAMINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti. min.		N Sex	E	I. µA	F.	P.W. msec	T.D msec
Domino, E F. and Olds, M. E. 1972										
Olds, M. 1972 b	0.25	i.p	+30 à 40	a. lateral hypothalamus	6/8 ♂	B	40-60	60 ♀	-	250
d-amphetamine	0.50									
	1 0			b. lateral hypothalamus	-					
	2.0									
	4 0			c. lateral hypothalamus	-					
	8.0			d. MFB	10 ♂					
Phillips, A G and Fibiger, H C 1973										
d- & l-amphetamine	a. 0 10	i. p.	+ 15	MFB	6 ♂	B	T > 5	60 ♀		200
	0.25			Subst. nigra (SN)	5 ♂		< 100			
	0. 50									
	1 00									
	b. 0. 50									
	1.00									
	2. 50									
Ritter, S., Stein, L. 1973	0.1	i. p.	+ 30	locus coeruleus	8-16 ♂	B	8-40	100 pps mono-phasic	0.2	1
	0.5		or							
d-amphetamine	1.0		+ 60							
Liebman, J.M., Butcher, L.L. 1974										
d-amphetamine	0.1	i.p	- 15	1 lat. hypothalamus (LH)	♂	2xB	60	60 ♀	-	200 every 2 sec.
	0.25			1 substantia nigra (SN)						
	1.0									
l-amphetamine	0.25									
	1.0									
	2.5									
Atrens, D.M. et al. 1974	0.5	i.p.	- 30	- paraventricular hypothalamus (n=6)	38 ♂	B	5-60	50 ♀		
	1.0			- medial hypothalamus (n=17)						
	2.0			- lat. hypothalamus (n=9)						
	6.0			- thalamus (n=6)						
AMPHETAMINE										
Atrens, D.M. et al., 1974										

SESSION		RESULTS	REMARKS
Dur min.	Proc		
		Partial protection ↔ tetrabenazine (80') Full protection ↔ chlorpromazine (80'). Partial protection ↔ physostigmine (80'). No protection ↔ pentobarbital during depress., after incapacitation ↗ .	
30-45 + 80	CRF	a. high SS (750-1200 R/8 min): insign. changes by 0.25 mg/kg, 4.0 and 8.0 mg/kg ↓ sign. at 16 and 24 min b. 2.0 mg/kg ↑ on low SS (100-350 R/8 min) c slight ↑ and subsequent ↓ in moderate SS (350-750 R/8 min) d non-SS: 2 mg/kg ↑ onset 32 min., duration > 80 min.	
2 x 15 20 - 30 interval	CRF	MFB: - d-amphetamine, moderate ↑ at 0.1 mg/kg; sharp ↑ from 0.25 to 1.0 mg/kg - l-amphetamine less effective: sign difference at 0.5 and 1.0 mg/kg Ratio d/l: 7-10/1 SN Effects d- & l-amphetamine similar	
120	CRF	↗ % of pre-drug 0.10 mg/kg: ± 180 % 0.25 mg/kg: ± 320 % 0.50 mg/kg: ± 390 % 1.00 mg/kg: ± 270 %	Fig. and cumulative records
2 x 14	-	1. SS - period 2 (not period 1): d- and l-amphetamine ↗ in HL - period 1 + 2 (0.25, 1.0 mg/kg): d-amphetamine ↗ SS (not sign. with l-amphetamine) 2. Number of crossings (one side to the other), non-sign ↗ except 2.5 mg/kg of l-amphetamine in HL-group	Rate-free index of SS: every 2 sec. 1 S in one of the sides of the cage Sides where S is on switching at intervals of 1, 2 or 3 min. Total session: 2 periods of 14 min.
		- Rate-free index of reward (moving from one side to the other in a shuttle box) (2.5-min periods). - 18 rats run at three different current levels (M) during 15 min (5 min warm-up). 1)	Escape behaviour also recorded.

	Increase	No change	Decrease
PaH (n=6)	6	0	0
MH (n=17)	17	0	0
LH (n=9)	6	2	1
Th. (n=6)	2	0	4
Total 38	31	2	5

	2) 4 medial subjects only showing escape behaviour: under the influence of amphetamine, reversal to SS (in 3/4 rats permanent). 3) Dose response (n=12), asymptotic. 0.5-1.0 mg/kg, decrease to initiate SS 2.0 mg/kg, no further decrease 4.0-6.0 mg/kg: deleterious effect	

IMIPRAMINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti.		N Sex	E.	I. µA	F.	P.W. msec.	T.D msec
Stein, L., Seifter, J. 1961	5.0 15.0	i.p.	-15 min.	- post. hypothalamus - midbr tegmentum	7 ♂	B	100-250	100 pps	0.2	150
Stein, L. 1962 a	3.5 5.0 10 15 40 90	i.p.	-15 min.	- post. hypothalamus - anter. midbr. tegmentum	6 ♂♀	B	100-250	100 pps	0.2	150
Stein, L. 1962 b	5 0 10 15	i.p.	-	-post. hypothalamus -anter. midbr. tegmentum	7 ♂	B	0-450	100 pps	0.2	150
Stark, P. et al 1969	3.0 10 20	i.p.	-15 -150 min.	septal area anteromid hypoth post. hypothalamus midbr. tegmentum	>3 ♂ >3 ♂ >3 ♂ >3 ♂	B	T = 15 T = 15 T = 20 T = 20	60 %	-	250
Benešova, O. 1969	5.0	i.p.	+30 min	lat. hypothalamus (MFB)	1 ♂	B	40-100	50	-	500
AMITRIPTYLINE										
Stein, L. 1962 a	3.5 10 30	i p.	-15 min.	post. hypothalamus ant. hypothalamus	♂	B	100 250	100 pps	0.2	150
Stein, L 1962 b	20	i p.								
Benešová, O. 1969	2.5	i.p	+30 min	lat. hypothalamus (MFB)	♂	B	40-100	50 %	-	500
NORTRIPTYLINE										
Stark, P. et al. 1969	1.0 3.0 10.0	i.p.	15 and 150 min.	septal area anteromid. hypothalamus post. hypothalamus midbr tegmentum	> 3 ♂ > 3 ♂ > 3 ♂ > 3 ♂	B	T = 15 T = 15 T = 20 T = 20	60 %	-	250

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
> 120-180	CRF	- Potentiation of 0.25 mg/kg d-methamphetamine (pretreatment 10 min.) - Pretreatment chlorpromazine (3.0 mg/kg) and imipramine before amphetamine antagonism	One example of representative animal
> 180	CRF	- Large doses depress SS - Potentiation of methamphetamine (0.25 mg/kg) Doses > 20 mg/kg: reduction in the magnitude of potentiation Very high doses diminish response to amphetamine - No potentiation of cocaine	Examples of cumulative records
120-360	CRF	- 10 mg/kg raised threshold - moderate doses potentiate and prolong amphetamine eff. Effect > than increase by doubling amphetamine	Two lever situation: one lever (stimulation lever) SS and stepwise decrease in intensity, second lever (reset lever) resets current to top value
10 + 4 x 10	CRF	Ten minute periods at T (= threshold intensity) T-1, T+1, T+2 (+ 1 = 5 µA) - Effect on threshold: 0 or raises - ↓ most pronounced with 20.0 mg/kg in anteromiddle hypothalamus	
240	CRF	1.5 mg/kg i.p.: no effect or slight ↘ Potentiation of effect cocaine (5.0 mg/kg i.p.)	No data One example
> 180	CRF	Potentiation of 0.25 mg/kg d-methamphetamine by 3.5 and 10 mg/kg. Diminution of d-methamphetamine effect by 30 mg/kg.	One cumulative record
		Two lever situation (see imipramine) Augmentation of d-amphetamine (1.5).	One example
240	CRF	2.5-5.0 mg/kg i.p. · no effect Potentiation of effect cocaine (5.0 mg/kg i.p.)	One example of 2.5 mg/kg effect
10 + 4 x 10	CRF	Post. hypothalamus and ventro-tegmental animals lowering threshold and decrease in high rates of responding.	

IPRONIAZID					RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti min	BRAIN STRUCTURE	N Sex	E	I µA	F	P W msec	T D msec.
Stein L 1962 a	100	i p	0	midbr tegmentum	1 ♂	B	100 250	100 pps	0 2	150
Stein L 1964 a 1967	a. 100	i p	0	hypothalamus midbr tegmentum	1 ♂	B	T	100 pps	0 2	150
	b 25	i p	-22 5 hrs		1					
	c 100	i p	+60		2					
Poschel B P Ninteman F W 1964	100	i p	0	post lat hypothalamus		M	40	60 ♂		400
Haley T J et al 1968	40	i p		dorsomed nucleus MFB lat hypothalamus ventromed hypothalamus	3 ♀ 2 ♀ 1 ♀ 1 ♀	B				
ETRYPTAMINE										
Stein L 1962 a	2 5	i p	0	midbrain tegmentum	1 ♂	B	100 250	100 pps	0 2	150
Poschel B P Ninteman F W 1964	4 0	i p	+1 5 hrs	post lat hypothalamus	♂	M	40	60 ♂	-	400
PARGYLINE										
Poschel B P Ninteman F W 1964	50	i p	+1 5 hrs	post. lat hypothalamus	♂	M	40	60 ♂	-	400

SESSION		RESULTS	REMARKS
Dur. hr	Proc.		
>3	CRF	1 example of potentiation methamphetamine (0.25 mg/kg) long pretreatment interval necessary. 80 min. 24 hrs later still potent	
>2	CRF & VI	a. ↓ SS	
	1 min. FI	b. Daily (8 x) injections small erratic ↑	
	CRF & VI	c. Stim. effect of phenethylamine (1.0, 2.5 or 10 mg/kg) 2.5 hrs after iproniazid	
6	CRF	↑ SS after two daily inj iproniazid 1-2 hrs delay	1 example
1	CRF	10 daily injections 3/8 rats ↗ during drug ↓ 8th day post-administration	
180	CRF	- No stimulating effect - Before d-methamphetamine (0.25 mg/kg) similar potentiation as with iproniazid	1 example
360	CRF	Immediate ↑	1 example (amphetamine-like properties)
360	CRF	↑ SS. delay of 1 to 2 hrs	1 example

TRANYLCYPROMINE					RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti min	BRAIN STRUCTURE	N Sex	E	I µA	F	P W msec	T D msec
Stein L 1964a										
Poschel B P Ninteman 1964	2 0	i p	+1 5 hr	post lat hypothalamus	6 ♂	M	20 30	60 $\frac{q}{s}$		400
Poschel B P 1969	2 0 3 0	i p	30	mapping telenceph hypothalamus mesencephalon	65 ♂	M	10 to 50	60 $\frac{q}{s}$		400
Stinus L et al 1971	5 0	i p	20	ventral tegmentum lat hypothalamus	13 ♂ 11 ♂		T (?)	100 $\frac{q}{s}$		200
COCAINE										
Stein L 1962 a	4 0 5 0	i p	+30	midbr tegmentum post hypothalamus	2 ♂ 1 ♂	B	100 250	100 pps	0 2	150
Benešová O 1969	5 0	i p	+60 or +180	lat hypothalamus (MFB)	♂ ♂	B	40 100	50 $\frac{q}{s}$		500
Crow T J 1970	5 0	i p	+60	ventral midbr tegmentum	7 ♂	B		100 $\frac{q}{s}$	0 5	200

SESSION		RESULTS	REMARKS
Dur. hr	Proc.		
		Moderate increase, for a short time after injection	No data
6 or >	CRF	↑, 1-2 hr delay	1 example
5.5	CRF	First post-hour injection not counted Largest ↑ : MFB, supramammillary decussation, ventral tegmental area of Tsai, tissue directly over interpeduncular nucl. No correlation between SS-rate and ↑	
5	CRF	20 minutes after injection and during 5 hrs sign. ↑ ↑ effects greater in ventral tegmentum area Pretreatment with PCPA (parachlorophenylalanine), 350 mg/kg, 24 hrs no change in ↑ effects.	
180	CRF	Intrinsic action weak ↑ 5.0 mg/kg clear ↑ of d-methamphetamine (0.25 mg/kg) given 10 min after cocaine, but not in less responsive animal No potentiation of 10 mg/kg imipramine	
240	CRF	Intrinsic action ↑ Potentiation of effect of atropine (5.0 mg/kg), imipramine (5.0 mg/kg) and amitriptyline (2.5 mg/kg)	3 representative cumulative records
120	CRF	Reduced current (control rates 50-3000 R/hour) in CRR 948, cocaine 1943, difference 994 (± 196)	

MESCALINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETERS				
REFERENCES	Dose mg/kg	Rte	Ti min		N Sex	E	I µA	F	P.W. msec	T.D. msec
Bailey, P.T., Pradhan, S.N. 1972 (see also Pradhan, S.N., 1974)	6.3 12.5 18 25 25			post. lat. hypothalamus	10 ♂ 4 ♂	B	rms	60 ⌇	-	400
LSD										
Olds, J. et al, 1957 Olds, J. 1959	0.2	i.p.	0	septal, preoptic post. ventr. hypothalamus sub-septal middle hypothalamus	♂	B	30-55	60 ⌇		500
Pradhan, S.N. 1974	200 1									
Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC)										
Bailey, P.T., Pradhan, S.N., 1972 (see Pradhan, 1974 = same)	1 5 10 15 20	i.p.	0	post. lat. hypothalamus	13 ♂	B	T	60 ⌇	-	400
	1 5 10 15 20 10 15 20	i.p.		post. lat. hypothalamus	13 ♂ 2 ♂ 1 ♀ 1 ♂	B	rms ≥T	50 ⌇	-	400

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
6 x 10 120-150		- % change from control (mean ±S.E.) 6.3 mg/kg. -11 ±8 n animals ↓ 7/10 12.5 mg/kg -44 ±9 n animals ↓ 9/10 18 mg/kg. -54 ±8 n animals ↓ 10/10 25 mg/kg: -70 ±7 n animals ↓. 10/10 - Onset. 10 min, peak effect. 30-40 min. - 3/5 rats biphasic response initial ↓, thereafter ↗ over normal. Daily injection for 11 days - 1st injection marked ↓ - Development of tolerance. return to control or slight ↗ within 7 days.	Lack of cross-tolerance to Δ^9-TAC in mescaline-tolerant rats.
6 x 8	CRF	1. Pronounced ↓, largest during second 8-min period (at 35 µA). 2. Serotonin (0.9 mg/kg) 1/2 hr before LSD - antagonism of ↓ in septum, preoptic and post. ventr hypothalamus - no antagonism other regions 3. Brom-LSD ↓ in sub-septal and middle hypothalamus.	Each 8-min period, increase current by 5 µA.
		- Inhibition from 7-94 % in 80 % of cases - No clear dose-response - Threshold study only periodic cessation.	No details. 1 example.
- 90	CRF	- % change from control (mean ± S E) 1 mg/kg -16 ± 9 n animals ↓ 6/13 5 mg/kg -17 ± 7 n animals ↓ 8/13 10 mg/kg -36 ± 9 n animals ↓10/13 15 mg/kg -35 ± 8 n animals ↓12/13 20 mg/kg -32 ± 9 n animals ↓11/13 - Decrease starts 10-20 min - Persistent ↓, peak at 10-20 mg/kg, duration at 10 mg/kg (n=7) 4-8 hrs Daily injection: - max ↓ after 1-3 days - tolerance within 7 days (return to baseline or above)	- Lack of cross-tolerance to mescaline in Δ^9-THC-tolerant rats. - Lack of cross-tolerance to Δ^9-THC in mescaline-tolerant rats.

ARECOLINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti		N Sex	E	I μA	F	PW msec.	TD msec.
Olds, M E. and Domino, E F 1969 a	0.1 0 4 0.8 1.6 2.0 3.0	s.c.	+ 30 min	lat post hypothalamus	6-14 ♂ per dose	B	40-60	60	-	250
Olds M E and Domino, E F 1969 b	0.8 1.6 2.0 3.0	s c.	+ 30 min	post lat hypothalamus	7-14 ♂ per dose	B	40-60	60	-	250
Fradhan, S.N. and Kamat, K A 1972	0.5 1.0 2.0	i p	0	lat post hypothalamus post hypothalamus	-	B	-	60	-	400
PILOCARPINE										
Newman L M. 1972	0.5 1.0 2.0 4.0	i p	-3	lat. hypothalamus post hypothalamus	3 ♂ 3 ♂	B	75 rms or >	60	-	200
NEOSTIGMINE										
Jung, O H. and Boyd, E S 1966	0.05	i p	-15	area from middle hypothalamus to anter commissure	9 ♂	B	T= 15-25	60	-	450
Domino, E F. and Olds, M E 1968	40.5 81 162 202.5 243 μg/kg	s.c.	+30	lat. hypothalamus	4-6 ♂ per dose	B	40-60	60	-	250
Olds M E., Domino, E.F 1969 b	80 5 161 μg/kg	s c	+30	post.lat. hypothalamus	12 ♂	B	40-60	60	-	200
Newman L M 1972	0 025 0.05 0.1 0.2	i p	-3	post.hypothalamus lat. hypothalamus	4 ♂ 2 ♂	B	75 rms or >	60	-	200
Pradhan, S N. and Kamat K A 1972	0.05 0.1	i.p	0	lat, post. hypothalamus post.hypothalamus	4	B	-	60	-	400

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
30 +80	CRF	- ↓ SS, short latency, peak ↓ at 8-16 min., quick recovery. Mean rate of SS: 15 % (1.6 mg/kg) - 56 % (0.1 mg/kg). - Antagonism (antagonist, s.c., -30 min.) · mean rate after pretreatment: scopolamine (0.5 mg/kg). 125 % methscopolamine (0.5 mg/kg): 32 % mecamylamine (5.0 mg/kg): 11 % trimethidinium (5.0 mg/kg): 42 %	
30+80	CRF	- At 16 min.: ↓ fR %: 15 % (1.6 mg/kg)-39 % (3.0 mg/kg) - At 64 min.: recovery to 2/3 of control rates (63-78 %)	
60	CRF	↓ SS	
6 x 10	VI 30 sec.	Time-dose related response ↓ , peak at 20-30 min., followed by recovery Post. hypothalamus: more sensitive % of control (6 rats together) at 20/30 min 0.5 mg/kg: ± 85-75 % 1.0 mg/kg: ± 65-75 % 2.0 mg/kg: ± 60-60 % 4.0 mg/kg: ± 35-35 %	
5 periods	CRF	No change from control range	
30+32	CRF	40.5 µg/kg: 0 effect 81 µg/kg small ↓ (72 % control rates), short duration: 16-24 min. > doses, greater ↓	Also cholinergic-induced crisis (2/6 subj. +)
30+80	CRF	Peak effect 8 min., 85.5 µg/kg: 73 % of control, 161 µg/kg. 63 % of control	
6 x 10	VI -30 sec.	0.025 mg/kg: sign. ↑ at 20-60 min. in 3/4 post. hypothalamic rats and 1/2 lat. hypothalamic rats Other doses: 0 effect	
60	CRF	0.05 mg/kg: ↓ : % change from control: for the individual animals: -89, -95, -28, -58 0.1 mg/kg: marked ↓	

PHYSOSTIGMINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti min		N Sex	E	I μA	F	P W msec	T D msec
Jung O H and Boyd E J 1966	0 1 0 2	i p	15	area from midbr hypothalamus to anter commissure	9 ♂	B	T 15 25	60 $_{b}$		450
Domino E F and Olds M E 1968	12 5 25 50 100 200 μg/kg	s c	+30	lat hypothalamus	4 6 ♂ per dose	B	40 60	60 $_{b}$	-	250
Olds M E and Domino E F 1969 a	50 to 300 μg/kg	s c	+30	post lat hypothala mus	22 ♂	B	40 60	60 $_{b}$		250
Olds M E and Domino E F 1969 b	50 100 200 300 μg/kg	s c	+30	post lat hypothala mus	32 ♂	B	40-60	60 $_{b}$	-	250
Malick J B and Goldberg M E 1970	0 4 0 8	i p	15	post lat hypothala mus	4 ♂ 8 ♂	B		100 cy/sec	0 2	300
Newman L M 1972	0 05 0 1 0 2 0 4	i p	3	post lat hypothala mus	5 ♂ 3 ♂	B	75 rms or >	60 $_{b}$		200
Iradhan S N and Kamat K A 1972	0 05 0 1 0 2	i p	0	lat post hypothala mus post hypothalamus	5 ♂	B	a 25-48 b < 45	60 $_{b}$		400
Olds M Ito M 1973	0 2	i p	+30	post lat hypothala-mus	28 ♂	B	5 V	80 pps	0 3	250

SESSION		RESULTS	REMARKS
Dur min	Proc		
5 x 5	CRF	Effect on T T+5 T+10 T+20 T+25 µA - 3 rats 0 1 mg/µg some ↑ at T (not sign) 0 2 mg/kg ↓ at T and T +10 - 5 rats 0 1 mg/kg sign ↓ - 1 rat no effect	
30+32	CRF	-12 5 and 25 µg/kg 0 effect -50 µg/kg ↓ m 25 % (indiv variability) -100 µg/kg all subj ↓ >50 % - > doses prolonged effects	
30+80	CRF	% of control rate ↑ at 32 min after injection 50 µg/kg 76 9 (P< 2) 100 µg/kg 49 9 200 µg/kg 17 0 300 µg/kg 4 4 (all P< 001) Onset 8 16 min peak effect 24 to 40 min	
30+80	CRF	Dose dependent ↓ 20 % (50 µg/kg) 95 % (100 µg/kg) Peak effect 32 min	Ineffective in escape behaviour
60	CRF	0 4 mg/kg slight ↓ (not sign) 0 8 mg/kg ↓ (sign) control/drug 5561 ± 598/2769 ± 958	Mean ± S E 8 rats
6x10	VI 30 sec	Dose and time related ↓ at 20 min with 0 4 mg/kg 0 1 mg/kg moderate ↓ peak at 20 30 or 40 min	
6x10	CRF	a Constant current throughout session (2 subj) b Stepping up current (each step +6 µA up to 48 µA each 10 min) 0 05 mg/kg ↓ % change from control in indiv anim -17 45 35 36 23	
30 30 45	CRF	1° period (30 min) SS 2° period (30 min) injection physostigmine ↓ at 15 à 30 min 3° period (45 min) injection scopolamine (0 5 mg/kg) reinstate SS	Correlated with neuronal activity

NICOTINE				BRAIN STRUCTURE	RATS		STIMULUS PARAMETER			
REFERENCE	Dose mg/kg	Rte	Ti. min.		N Sex	E	I µA	F	P.W. msec.	T.D. msec
Wanner, H.U., Sattig 1966	0.25 0.50	i.p.	-1	lat. hypothalamus (MFB)	5	M	40-120	200 pps	2	500
Bowling, C. and Pradhan, S.N. 1967	0.1 0.4	i.p.		hypothalamus		B				
Pradhan, S.N. et al. 1967	0.025 0.2	i.p.	-15	hypothalamus		B				
Olds, M.E. and Domino, E.F. 1969 a	25 50 100 200 400 600	s.c.	+30	lat. hypothalamus	7 or ♂ per dose	B	40-60	60 c/s	-	250
Olds, M.E. and Domino, E.F. 1969 b	0.4 0.6	s.c.	+30	post. lat. hypothalamus	7-8 per dose	B	40-60	60 c/s	-	250
Pradhan, S.N. and Bowling, C. 1971	0.0125 0.4	i.p.	0	post. lat. hypothalamus post. hypothalamus	a. 24 b. 15	B	a. T=25-100 b. < 48	60 c/s	-	400
Newman, L.M. 1972	0.1 0.2 0.4 0.8	i.p.	-3	lat. hypothalamus post. hypothalamus	3 ♂ 5 ♂	B	75 rms or >	60 c/s	-	200
Pradhan, S.N. and Kamat, K.A. 1972	0.05 0.10	i.p.	0	lat. post. hypothalamus post. hypothalamus	13 ♂	B		60 c/s	-	400
Continued										

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
2x2.5	CRF	Tested on high (H) and low (L) current % stimulation per minute NaCl Nic. (0.25) Nic. (0.50) H 82.2 87.2 80.2 L 44.8 75.4 73.8	Sequence of 2.5 min high current followed by 2.5 min low current (comparable effects with amphetamine).
		After prolonged period of SS when SS slowed down nicotine ↑ SS ⇔ phenobarbital (10-15 mg/kg) Less ⇔ reserpine (0.5-1.0 mg/kg) Reduced by pre-adm. mecamylamine (1-2 mg/kg)	
		SS ↑	No data
30+80	CRF	↓, but transient and variable m̄ control rate at increasing doses 108.7, 81.8, 46.5, 51.4, 32.5, 69.1 % After transient ↓, some facilitation at 200 ug/kg.	
30+80	CRF	↓ completely, though transiently m̄ % change 400 µg/kg 32.5 %, 600 µg/kg 69 % at peak effect (8 min.) At 64 min. ↑ 400 µg/kg 117 %, 600 µg/kg 110 % of control	
60 or 3-6x10	CRF	1. 100 or 200 µg/kg ↑ in rats with slow SS (800-1500 R/hr), ind. variability sometimes initial ↓. 2. a) Constant current at 1.12.5 µg/kg - 200 µg/kg, overall effect gradual ↑ from 3 % to 41 %, duration 50 min at 37.5 and 50 µg/kg and > 60 min. at higher doses. Second group ↑ 75 % at 50-400 µg/kg b) Stepping-up current: 6 µA period up to 48 µA 7 doses (20-400 µg/kg) Rats with high SS ↑ at low current Levels (18-24 µA), ↓ at higher current Rats with lower SS ↑, max at 30 µA, higher current ↓ No defin dose-response curves. Duration at 100 µg/kg 30-50 min. At baseline rate < 300 R/10 min · doses 50 µg/kg and > sign. rate-dose interaction 100 µg/kg ↑, injected after 9-10 hrs SS (SS reduced by 24-83 % of initial rate) No effect on unreinforced responding	
6x10	VI -30 sec.	SS ↑ directly related to time and dose No sign difference between placements No initial decrease. Sign. ↑ (onset 10) Pretreatment with mecamylamine (1.0 mg/kg) in 9 rats (5 post., 4 lat.) blockade of increase	
60	CRF	Constant current throughout session (5 rats), or stepping current (increase each 10 min. by 6 µA) (8 rats) % change (from controls 5 rats: 0 or slight ↓, 8 rats ↑ (range 10-54 %)	
		Pretreatment scopolamine (0.10, 0.25, 0.50, 1.00 mg/kg) enhanced facilitatory effects nicotine in 8 rats. In 5 rats with high resp. rate further ↓ or unaffected	

SCOPOLAMINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Ti min		N Sex	E	I µA	F	P W msec	T D. msec
Olds M E and Domino E F 1969 a	0 5	s c	+30	post. lat. hypothalamus	6 ♂ or ♀	B	40-60	60 ♂	-	250
Domino E F and Olds, M E 1972 Olds M E 1972 b	0 25 0 5 1 2 4 6 8	s c.	+30-45		6-8 ♂ per group	B	40-60	60 ♂	-	250
Newman L M 1972	0 4 0 8 1 6	s c	-3	post. hypothalamus	3 ♂	B	75(rms) or >	60 ♂		250
Olds M E 1972 a Olds M E 1972 b	0 5	s c	+30-45	MFB	8 ♂	B	40-60	60 ♂	-	250
Pradhan S N and Kamat K A 1972	0 05 0 1 0 25 0 5	i p	-10	lat post hypothalamus post hypothalamus	3 15 ♂ per dose 5 ♂	B		60 ♂	-	400

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
30+80	CRF	SS rate after pretreatment scopolamine (1/2 hr before the agonist): scop. + physostigmine (100 µg/kg): 105 % scop. + arecoline (1600 µg/kg): 125 % scop. + nicotine (600 µg/kg: 91 % Methscopolamine, no effect	
120	CRF	a. Groups with control rates 100-1200 R/8 min. 0.25 mg/kg: ↑ 14-27 %, 14-24 min. after injection Higher doses: mean effect ↓, max 16 min. 2 mg/kg: less ind. variability, mean ↓ less than 50 % b. 2 mg/kg No effect on low (100-350 R/8 min) or moderate SS (350-750 R/8 min). High SS (750-1200 R/8 min) ↓ 50 %, 8 min after injection, raise to 80 % of control, lasting 80 min session c. Slight facilitation in non-responders and naive rats, with peak at 16 min.	
6 x 10	VI-30 sec.	No sign. differences Individual data: 2 subjects ↑ at 1.6 and 0.8 mg/kg	Analysis of variance
1. 30-45 2. 32 3. 80	CRF	1. On 80 min. session, minor changes 2. 30-45 min. no drug 32 min. inj. scopolamine 80 min. inj tetrabenazine (2.0 mg/kg), chlorpromazine (2.5 mg/kg), physostigmine (0.1 mg/kg) or pentobarbital (10 mg/kg) Antag. depression tetrabenazine: sign. at 8, 16 and 24 min. Antag. depression chlorpromazine. protection throughout 80 min. session (sign. 16, 24, 32 min.). Antag. depression physostigmine full protection Antag. depression pentobarbital: potentiation initially, facilitation later (after 32 min.)	
6x10	CRF	a. Stepping-up current, increase each 10 min. with 6 µA (max. 48 µA), 6 x 10 min. b. Constant current throughout session a. Stepping-up current 0.1 mg/kg sign. ↑ (10/12 rats) higher doses ↓, less stimulating except at low SS rates b. Constant current. 0.05-5.5 mg/kg: sign. ↑, no dose-response, onset 10-20 min., peak 40-50 min. c. 0.25 mg/kg scopolamine 29 % ↑; 0.50 mg/kg scopolamine: 32 % ↑ methylscopolamine: 3 % ↓; 22 % ↓	

SCOPOLAMINE					RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti min	BRAIN STRUCTURE	N Sex	E	I μA	F	P W msec	T D msec.
(contd)					5 ♂					
Pradhan, S N and Kamat, K A. 1973	0 05 0.1 0 25 0.5	i p	-10	lat. post. hypothalamus post hypothalamus	6-20 ♂ per dose	B		60 ♂	-	400
ATROPINE										
Jung O H and Boyd, E S 1966	0.1 0.2	i p	-20	area from midbr. hypothalamus to ant. commissure	5 ♂	B	T= 15-25	60 ♂	-	450
Newman, L M 1972	2.0 4 0 8.0 16	i p	-3	post. hypothalamus lat hypothalamus	4 ♂ 3 ♂	B	75(rms) or >	60 ♂	-	200
Pradhan S N and Kamat, K A 1973	0.5 1.0 2.0 5 0	i p	-10	post. hypothalamus lat post. hypothalamus	4 ♂ to 15 ♂ per dose	B		60 ♂	-	400

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
		d. Complete antagonism of the ↓ of physostigmine (0.05 mg/kg) by scopolamine (0.1-1.0 mg/kg), no antagonism of neostigmine (0.05 mg/kg), methylscopolamine (1 mg/kg) complete or partial antag. of neostigmine.	
60	CRF	Stepping-up current and constant current (see 1972) Grouping of rats in low, medium, high SS ↑ in low resp. with 0.1-0.5 mg/kg ↑ in med. resp. with 0.1-0.25 mg/kg variable effects in high responders	
5	CRF	Effect at T (threshold), T +5 to 10, T+20 to 25 No sign. change (nor by methylatrop.) Pretreatment: complete blockade of ↑ effect, by physostigmine (0.1 mg/kg), no effect with methylatropine	
6 x 10	VI -30 sec	Sign. difference between placement and between doses. Sign. effects (% of control) - Lat. hypothalamus. 2.0 mg/kg. ↗ ± 115 % (60 min) 4.0 mg/kg ↗ ± 120 % (30, 40, 50 min) 8.0 mg/kg: ↘ ± 80-85 % (20, 30 min) 16.0 mg/kg: ↘ ± 80-90 % (30, 40, 50, 60 min) - Post. hypothalamus: 2.0 mg/kg. ↗ 100-105 % (50, 60 min) 4.0 mg/kg ↘ ± 80 % (20-60 min) 8.0 mg/kg idem 16.0 mg/kg. ↘ ± 80-55 % (10-60 min)	→Due to low saline base-line
60 or 6x10	CRF	Constant current through 60 min. session or increase in steps of 6 uA every 10 min. % ↑ from control: - stepping-up current: 1.0 mg/kg: 10 % (4/4 rats ↑) 2.0 mg/kg: 30 % (5/6) 5.0 mg/kg: 26 % (4/4) - constant current 0.5 mg/kg: 5 % (6/12) 1.0 mg/kg: 6 % (11/15) 2.0 mg/kg: 14 % (9/12)	Drug effects appreciable at low baseline rates less marked at higher rates (>700 R/10 min)

MORPHINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti.		N Sex	E	I μA	F	P W. msec.	T.D msec
Olds J. 1959	7 0	i p	-	anter forebrain MFB post midd, hypothalamus		B	10, 20, 30, 40, 50	60 %	-	
Olds, J , Travis, a R P. 1960	7.0	i p		septal region ant MFB post. MFB tegmentum	6/8 6/8 6/8 6/8	B	0, 10, 20, 30, 40, 50	60n_0	-	500
b	5.25 7 00 8.75 10 25	i.p		MFB	± 40	B				
Adams, W J et al 1972	10.	s c.	+ 10 min	lat. hypothalamus (MFB)	2x7 ♂	B	320-800	100 pps	0 1	200
Glick, S.D et al. 1973	0.5 ml of 50 mg/ml	s.c.	+ 5 hrs	MFB	6x4-6 ♂	B	30-80	60n_0	-	500
Lorens, S A , Mitchell C C 1973	5.0 10. 20.	s c.	+ 10 min.	lat. hypothalamus	4 x 8 ♂	B	240 - 880	100 pps	0.1	200
Lorens S A 1973	7 5	s c	-1	lat hypothalamus	4 ♂	B		100 pps	0.1	200
Blake and Halpern 1971	10 15	i p								
Marcus R , Kornetsky C 1974	4 8 12	s c.	-10	lat hypothalamus (MFB)	3 ♂	B	25-350	200 pps	0 2	500

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
8 + 5x8	CRF	Slight ↑ in ambivalent region (middle hypothalamus), ↓ in anter. forebrain, post. hypothalamus	2 examples
6 x 8	CRF	a. Mapping. Total effect 68 % ↓ of the time, 20 % ↑. Hypoth. region ↓. Sign. difference between septal region (↓) and tegmental area (↑) b. Dose response main effect ↓, more at 7.0 to 10.25 mg/kg compared with meprobamate	Only data at 30 µA level
6 x 10 at hr interval	CRF	5 daily injections. 1st day at 2 hrs ↓, at 5th and 6th hr ↑; 3rd day tolerance to suppressive effect, 5th day excitatory ↑ and apparent earlier.	
30	CRF	Repeated injection for 3 days. - during SS - during withdrawal Initially ↓ SS during dependence minim. withdrawal SS during dependence and withdrawal no effect on withdrawal SS during withdrawal SS ↑	Implantation of reservoir
6 x 10 at hr interval	CRF	5 daily injections - ↓ and ↑, develop. tolerance → excitatory effect appeared earlier and tended to rise - 5 mg/kg ↓ 1 hr, 2 hrs 0, 3 hrs ↑ complete tolerance 3rd day - 10 mg/kg ↓ 1 hr, ↑ 3rd and 4th hr - 20 mg/kg ↓ for 3 hrs, ↑ 5th and 6th hr	No correlation with wheel turning activity
2 x 10 at 1, 3 and 5 hrs		- ↓ and ↑ - Tolerance to suppressive effects 3rd day - No difference between SS lesion and control side	- Bilateral implantation - Rats lesioned unilaterally in locus coeruleus - Current adjusted up to 150 R/10 min
		Two phases 1. 90-150 min after injection time periods with no responding, when rat responds, response rate ≈ or ↑ 2. Rate exceeds control rates	Long periods of SS
30		- Threshold determination: 'staircase' procedure Procedure. 1 non-contingent S, R within 7 5 sec period followed by 1 contingent S - U-shaped dose-response curve 4 or 8 mg/kg ↓ threshold, > dose no effect	Comparison with threshold. Increasing effect on escape for negative S

DIPHENYLHYDANTOIN				BRAIN STRUCTURE	RATS	STIMULUS PARAMETERS				
REFERENCES	Dose mg/kg	Rte	Ti min		N Sex	E	I µA	F	P.W. msec	T.D. msec
Olds, M.E. 1970	75	i.p.		post. lat. hypothalamus		B		60 %	-	250
Weinrich, D., Clark, L.D. 1970	25 50	i.p.	30	MFB	12 ♂	B	50-100	175 200 pps	0.1	500
ACETAZOLAMIDE										
Weinrich, D., Clark, L.D. 1970	10	i.p.	60	MFB	12 ♂	B	50-500	175 200 pps	0.1	500
ALPHA-METHYL-PARA-TYROSINE										
Black, W.C., Cooper, B.R. 1970	200 400 600	or	-4 hrs	lat. hypothalamus (MFB)	8 ♂	B	300	200 pps	0.2 (interval 0.2)	250 every 1.5
Gibson, S., McGeer, E.G., McGeer, P.L. 1970 L-α-MPT DL-α-MPT	1. 75 2. 100 3. 200	i.p.		medial forebr. region of the post. hypothalamus	23 ♂	B	T 5-14 V	60 %	-	150
Cooper, B.R., Black, W.C., Paolino, R.M. 1971	200 600	or	+300	6 ♯· septal forebr. region (S-F) 6 ♯· lat. hypothalamus (LH)	12 ♂	B	300 and 500	200 pps	0.2 (+0.2 interval)	250
Stinus, L., Le Moal, M., Cardo, B. 1972	150	i.p.	+60	10 ♯. area ventr. tegmenti (AVT) 12 ♯· lat. hypothalamus (LH)	22 ♂	B	71.5±2.0 (AVT) 71.2±2.0 (LH)	200 cy	-	200

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
30+80	CRF	- Control rate in 8 min 365-1190. - ↓ to 60 %, 40 min after injection, still 50 % 80 min after injection. - No significant changes in extinction.	
10-min periods 10-min pauses	CRF	Slight ↓, 30 min after injection, ± 10 % with 50 mg/kg	Test at peak effect.
10-min periods 10-min pauses	CRF	Slight ↓, 60 min after injection, ± 10 % with 10 mg/kg	
-Rate-free test, 30 min lever-pressing, with 10 min interval. - Dose given in 3x1/3 at 0, 2 and 4 hrs. Data 1/2-10 hrs after injection.		- Rate free test every 2 min S on one side of the cage, randomly switched. - ↓ in rate free and lever-pressing situation. - Inverse relation stimulation rate and dose. - Wide range of individual differences.	
Drug experiment through day Voltage difference between control threshold and following drug administration, taken as drug-effect		- 18/23 rats ≠ in threshold 3 no effect, 1 decrease - Max effect 5-9 hrs after injection. - Recovery complete within 24-48 hrs - Increase voltage (n rats) +1.1 V: 1) 1; 2) 3; 3) 1 +2.2 V: 1) 1; 2) 2; 3) 0 +3.3 V: 1) 0; 2) 6; 3) 5	% of control NA: -; 25; 49 5HT: -; 65; 100
2x20 min with 10 min interval, 1° period 300 µA 1° period 500 µA Rate-free in shuttle box.		Main effect ↓, differed from each placement according to current intensity. Significant difference from control LH -300 µA between doses and control. -500 µA highest dose. S-F -300 µA doses from control, not between doses. -500 µA doses differ from each other and control	
8x30 min with 30 min intervals 8 control days. 9° day NaCl 10° day α-MPT 11,12,13° day control. Recording per 5 min.		1 Immediate ↓ 2. Partial recovery at start each period (especially 1st min). 3. Gradual decrease during session. 4 24 hrs later still ↓ AVT slightly higher 5 48 hrs complete recovery AVT, partially for LH	Effect on locomotor activity 1. Immediate ↓ (50 % of contr.) 2. 4 hrs later ↓ (19 % of contr.) (SS at that time 73 % of control).

ALPHA-METHYL-PARA-TYROSINE				BRAIN STRUCTURE	RATS	STIMULUS			PARAMETERS	
REFERENCE	Dose mg/kg	Rte	Ti min		N Sex	E	I µA	F	P.W. msec	T D msec
Beaugrand, J., St.-Laurent, J. 1973	100 x 3	i.p.	0 15 and 3 hr 15'	post. MFB or AVT	8 ♂	B	60	60 ϟ	-	250
Ritter, S., Stein, L. 1973	200	i.p.	-4 hr	locus coeruleus	6 ♂	B		100 pps	0.2	150
Stinus, L., Thierry, A 1973	150	i.p.	+60	22 # area ventr. tegmenti (AVT) 19 # lat hypothalamus (LA)	41 ♂	B	68 ± 2 (AVT) 73 ± 2 (LH)	100 cy	-	200
Stinus, L., Thierry, A., Blanc, G., Glowinski, J., Cardo, B. 1973	150	i p	+ 1 hr	area ventr. tegmenti (AVT)	24 ♂	B(2)	71 ± 2	100 cy	-	200
Yunger, L.M. et al. 1973	250	i.p.	-4 hr	lat hypothalamus	♂	B	356 ± 49 and 887 ± 82	200 pps	0.1	200
ALPHA-METHYL-PARA-TYROSINE										
Yuwiler, A., Olds, M.E. 1973	400	i.p.								
Stinus, L., Thierry, A. Cardo, B. 1974	50 75	i.p.	+1 hr	area ventr. tegmenti (AVT)	23 ♂	B(2)				

SESSION		RESULTS	REMARKS
Dur.	Proc.		
-10 min reading each 1/2 hr after base-line in 1/2 hr sessions 1 per day - 6 readings following 1st & 2nd injection after 12 hrs rest, 5 additional readings. - Thereafter L-dopa		- ↓ after 1st injection within 1st 1/2 hr - After 7 hrs SS completely abolished. - 24 hrs later recovery to less than half of controls - L-dopa reduction and subsequent recovery).	Spontaneous behaviour decrease of movements and hypotonia, drowsy. After 150 min slightly more active Back to normal after 12 hrs rest
		- ↓ of 42 5 % ± 9.5 %. - 2 rats with intraventricular cannula reversal suppressive effects by L-norepinephrine (10 µg) and not by dopamine.	
13 x 30 min, with 30 min intervals		1. α-MPT + Ro 04-4602 (50 mg/kg). gradual decline. 2. α-MPT + Ro 04-4602 + L-dopa (200 mg/kg) 4 hrs later reinstatement till end experiment in LH and AVT. 3. α-MPT + Ro 04-4602 + DOPS (400 mg/kg) 4 hrs later reinstatement till end experiment only in AVT, not in LA.	% control values NC DA 1. α-MPT 1 hr 84 * 79 * 4 hr 56 * 38 * 8 hr 39 * 26 * 2. α-MPT + L-dopa 4.5 hr 98 * 160 * 5 hr 92 * 290 * 8 hr 105 * 402 * 3. α-MPT + DOPS 5 hr 46 34 8 hr 35 31 (Each analysis 8 rats, * significant difference)
8 rats submitted to imposed bilateral S for 1 hr		No SS	- After α-MPT NE and DA significantly ↓ - Imposed stimulation acceleration NE utilization in brain stem, hypothalamus hippocampus and cortex - NE sign. reduced in rats not submitted to S - DA in striatum not accelerated.
-2x125 mg/kg α-MPT (4 hr interval). -Threshold SS 356 µA Threshold analgesia (pawlick) 887		Lever-pressing per 10 min Control / Drug 356 µA / 356 µA / 887 µA 1565 / 365 / 1098 ±131 / ±225 / ±285	
Non-contingent or forced S (no SS)		No self-stimulation.	Change in NE and DA in non-implanted, implanted (but not rewarding) and implanted (rewarding) with electrodes after forced S. Reduction in NE and DA in all groups
10 x 30 min with 30 min intervals		Rats lesioned by 6-OHDA in AVT, pedunculus cerebralis (PCS) others sham injected. α-MPT (50) 6-OHDA lesions enhances depressing effect in AVT (no significant difference in PCS). α-MPT (75) controls ↓ 52 % AVT and PCS ↓ 86 % (6th session).	

ALPHA-METHYL-META-TYROSINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETERS				
REFERENCES	Dose mg/kg	Rte	T1 min		N Sex	E	I μA	F	P W. msec	T.D. msec
Poschel, B.P.H., Ninteman, F.W. 1963	50	i.p.	+60	lat hypothalamus	3 ♂	M	20-30	60 ϕ	-	400
Poschel, B.P.H., Ninteman, F.W., Stanat, S.C 1965	10 25 50	2 s.c. 1 i.p.	+180	post lat. hypothalamus (MFB)	3 ♂	M	25-30	60 ϕ	-	400
DIETHYLDITHIOCARBAMATE										
Wise, C.D., Stein, L. 1969	2 mg in 25 μl	i. vent.	+30	medial forebr. bundle		13	100-400	100 pps	0.2	150
DISULFIRAM										
Wise, C.D., Stein, L. 1969	200	i p.	+60	medial forebr. bundle		B	100-400	100 pps	0.2	150
Roll, S.K 1970	100	i p	+60	medial forebr. bundle	3 ♂	M				150 or 800
Liebman, J.M., Butcher, L.L. 1973	150	i.p.	-360	mesenceph. central gray lat. hypothalamus	4 ♂ 11 ♂	2xB	15-40	60 ϕ	-	100
FLA-63 /bis(1-methyl-4-homopiperazinyl-thiocarbonyl disulfide/										
Stinus et al, 1973	40	i.p.		17 implanted area ventralis tegmenti (AVT)	24 ♂	B	71 ± 2	100 cy	-	200
Lippa, A.S. et al, 1973	25	i.p.	-7.5 hrs	post. hypothalamus	4 ♂	B		200 pps	0.2	300

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
7 + 8 hr session		- α-MMT no effect. - 1 hr before parnate (1 mg/kg) ≠ for > 3 hrs - 3, 5 hrs before test α-MMT, parnate (1 mg/kg) + tetrabenazine (2 mg/kg)· SS ↓.	1 example.
+1 hr 2≠ tranyl-cypro-mine (1 mg/kg) i.p. 1 ≠. pargy-line (20 mg/kg) s.c.		1° period (3 hr 15'): control, no visible effects of MAO-inhibitors. 2° period (3 hr 15') excitation on increasing doses. 10 mg/kg less than control 25 mg/kg ± 25 % 50 mg/kg· ± 3 x control	
SS for several hrs at an intensity maintaining stable responding		↓, off in 30-45 min.	Intraventricular injection of l-norepinephrine (5 µg) reversed suppression, not with d-norepinephrine (5 µg), dopamine (5 5 µg) or serotonin (4.8 µg). % of control SS rate diethyld. 9.7 ± 4.2 diethyld. + l-NE 66.1 ± 15 8
SS for several hrs at an intensity maintaining stable responding (32 experiments)		↓ between 7.0 % and 20.8 % of control. Neurohormones administered 1-3 hrs after disulfiram.	Intraventricular (10 µg) of l-(5 µg) or dl-norepinephrine reversed to respectively 62 5 ± 11.0 and 61.9 ± 8.8 % of control No reversal with α-NE, DA, 5 HT l-NE (injected i.p.).
5 hr session on 150 msec (1) or 800 msec (2) duration		↓ bar-pressing result from increase in frequency and duration of pauses. Replacement on the bar sufficient to induce resumption of SS. Pooled data (means 3 rats) m rates of responding (5 min). control / disulfiram / disulfiram without pauses (1) 171 / 102 / 152 (2) 359 / 263 / 347	
1° period: int. yielding 70-50 % of SS. 2° period: doubling current.		1° period ↓ SS. 2° period doubling current restored lever-pressing to an average rate exceeding control rates.	
8 rats submitted to imposed bilat. S for 1 hr		No SS	After Fla-63 - NE levels ↓ 1 hr after administration. - Imposed S marked acceleration of NE utilization in brain stem, hypothalamus, hippocampus, cortex. - NE ↓ (30-45 %) of when compared with rats not stimul.
		Fla-63 vehicle: 96 % of mean SS rate (3 days) Fla-63 88 % (no sign. difference)	

L-DOPA				BRAIN STRUCTURE	RATS	STIMULUS PARAMETERS				
REFERENCES	Dose mg/kg	Rte	Ti min		N Sex	E	I µA	F	P.W. msec	T.D. msec
Kadzielawa, K. 1973, 1974	100	i.p.		post.lat. hypothalamus	♂	B	30-70	50 ⅌	-	400
Liebman, J.M., Butcher, L.L. 1973	75 150	i p.	-30	mesenceph. central gray lat.hypothalamus	12 15	2xB	15-40	60 ⅌	-	100
Beaugrand, J., St -Laurent, J. 1973	50 and 200	i.p.		post. MFB or AVT	80 ♂	B	60	60 ⅌	-	250

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
4 cycles of 2400 R		L-dopa after 50 mg/kg Ro 4-4602 i.p - Intense ↗ during 45 min tested in 12 experiments 150 %. - Lasted 60-90 min. - In most experiments preceded by 30 min slowing or blockade	- No potentiation with desimipramine 2 mg/kg - No antagonism with 3-5 mg/kg phenoxybenzamine - Attenuation or prevented by 0.05 mg/kg haloperidol - L-α methyl-dopa (300 mg/kg i.p.) mild ↘ 2-3 hr after injection, for 2 hrs
L-dopa together with (-30 min) Ro 4-4602 (50 mg/kg). 1° period: SS at 50-75 % of max 2° period: SS at double current of period 1		- 1° period ↘ SS - 2° period doubling current restoring SS to levels not different from baseline rates. - In each group: 3 rats failed to initiate lever-pressing. After imposed S (30 S) restoration SS.	
-10 min readings after 1st injection 4 after the second (1 hr later). - Rats were treated (3x100 mg/kg) with α-MPT, 20 h 15' before		- α-MPT decreased SS, after 12 hr rest 5 readings of 10 min at 30 min intervals SS at ± 1/2 control values. - L-dopa ↘ within 1st 1/2 hr, following 1/2 hr value before injection. 2nd injection same pattern ↘ and subsequent recovery, but completely abolished 2 hr after 2nd injection 2 days later complete restoration	Spontaneous behaviour 1, 5 mg/kg less spontaneous movements, no hypotonia 2 200 mg/kg 20 min later polypnoea, 2 rats hypersalivation, 1 gnawing - hypoactivity

APOMORPHINE				BRAIN STRUCTURE	RATS	STIMULUS PARAMETER				
REFERENCE	Dose mg/kg	Rte	Tl. min.		N Sex	E	I μA	F	P W. msec.	T.D. msec
Liebman, J.M. and Butcher, L.L. 1973	0.75 1.50	i p	-15	lat.hypothalamus mesenceph control group	15 ♂ 9 ♂	2 B	15 - 40	60 ⚲	-	100
St -Laurent,J et al 1973	0 25 0 50	i p	+240	post lat hypothalamus	8 ♂	B	100 (37.5 RMS)	60 ⚲	-	250
Brockkamp, C L E and Van Rossum, J M 1974	0 1 0,2	s c	+30 -45	- nucl accumb - lat hypothalamus - cell-group A_9-A_{10} - locus coeruleus	29 ♂	B	100 300	100 cy	0 2	350
Kadzielawa, K 1974	0,4-1 0	i p		post.lat hypothalamus (MFB)	35 ♂	B	15-70	50 ⚲	-	400
Liebman, J M., Butcher L L 1974	0 25 0 50 0 75 1 5	i p	-15	lat hypothalamus (LH) substantia nigra (SN)	♂	2xB	8-40	60 ⚲	-	every 2 sec 200 msec
PHENTOLAMINE										
Hastings, L. Stutz, R M. 1973	5	i p	-15	traject MFB	14 ♂	B	T + 5-10	60 %	-	300
Lippa et al 1973	50 100 ug	IVL	-15	post hypothalamus	4 ♂	B		200 pps	0 2	300
PHENOXYBENZAMINE										
Bailey, P T. et al 1972	1-4	i p.		post lat.hypothalamus		B				
Kadzielawa K. 1973	3-5			post lat hypothalamus	♂	B	15-70	50 %	-	400
PROPANOLOL										
Bailey et al. 1972	0 5 2.0	i p.		post lat hypothalamus		B				
Hastings, L . Stutz R M 1973	10	i.p	-15	traject MFB	14 ♂	B	T + 5-10	60 %	-	300

SESSION		RESULTS	REMARKS
Dur. min.	Proc.		
20+ 10-15	CRF	Current used: 20 min at current which yields ± 50-75 % of maximal - 10-15 min.: at twice base-line current Apomorphine: ↓, more variable with 0.75 mg/kg Doubled current: - no ↑ at 1.5 mg/kg - ↑exceeding base-line at 0.75 mg/kg	
8x30	CRF	- α-methylparatyrosine (α-MPT) 100 mg/kg ↓ SS - Apomorphine (A), regardless pre-treatment: 0.25 mg/kg ↓ 1/2 hr 0.50 mg/kg ↓ 1 hr After 1 hour: V-A 0.25 or V-A 0.50 > α-MPT - A 0.25 or α-MPT - A 0.50	Session: 1 30 min free SS 2. inj. α-MPT or vehicle (V) 3. 30 min SS 4. 2 1/2 hr rest 5. 30 min SS 6. at 4 hr inj apomorphine or vehicle 7. readings 4 hr 10, 4 hr 40, 5 hr 10, 5 hr 40, 6 hr 10, 6 hr 40, 7 hr 10
	CRF LH: FR_4	- 14/29 rats ↑, 13 ↓ - At 100 ug/kg: ↓ 69.1 ± 22 % - Rats with ↑ (n=6): persistent responding (25-30 min) - A_9-A_{10} rats (n = 5): 0-current: persistent responding (22-30 min)	- Monophasic positive current - Submaximal response rate - No difference according to implantation site
	CRF	- Threshold effect 0.4 mg/kg - 1 mg/kg: ↑45 %, 5-60 min - 0.5 mg/kg ↔ haloperidol 0.1 mg/kg	Session 4-6 cycles of 2400 re-sponses
2x14		1. SS 0.25 mg/kg: SS in HL ↑, period 1 (no difference period 2) > SS in SN 0.50 mg/kg (period 1 + 2) SS in HL > SS in SN no sign difference from baseline 0.75 and 1.5 mg/kg SS ↓ in SN and HL, no difference SN-HL 2. Number of crossings (one side to the other), Sign. difference from baseline. HL SN 0.25 ↓ 0 0.50 ↓ ↓ 0.75 ↓ ↓ 1.50 ↓ ↓	Rate-free test of SS every 2 sec 1 S in one of the sides of the cage, switching at intervals of 1, 2 or 3 min Two periods of 14 min in total
C=30 D=30	CRF	- Mean responses (± S.E.) - base day 1622 ± 174 - drug 1271 ± 240 ($p < .05$)	C = control D = drug 15 min pause
30	CRF	- On normal rats no effects. - On pretreated rats, slight ↓ range 0-31 %, 50 µg mean 11 % 100 µg mean 13 %	Rats pretreated with 2 x 200 µg 6-OHDA. Tested after recovery.
		- Decreased responding. - Prevented or reduced amphetamine- or cocaine facilitation in ± 50 % of the subjects.	No data.
	CRF	Increase in the rate after Dopa not antagonized.	
		- Decreased responding. - Prevented or reduced amphetamine- or cocaine-induced facilitation in 50 % of the subjects	No data.
C=30 D=30	CRF	Mean responses (± S.E.) - base day 1398 ± 133 - drug 1431 ± 164 ($p < .05$)	C = control D = drug 15 min pause

N N DIMETHYLTRYPTAMINE					RATS	STIMULUS PARAMETERS				
REFERENCES	Dose mg/kg	Rte	Tl min	BRAIN STRUCTURE	N Sex	E	I μA	F	P W. msec	T D msec
Rosen A J Kuboe, K L. 1973	0625 .125 250 500 1 00 1 50 2 00	i p	0	MFB lat hypothalamus	3 ♂	B	80-150	100 300 cps	2	250-300
5 HYDROXYTRYPTAMINE										
Poschel B P H , Ninteman F W 1968	2 5-5 0 10 20 200	i p		MFB rostral to mammil lary bodies	♂	M	17 5-25	60 %	-	400
5 HYDROXYTRYPTOPHANE										
Kadzielawa K 1973	100	i p		post lat hypothala-mus	7 ♂	B	15-70	50 %	-	400
Host S et al 1974	28 57 115	i p	0	post lat hypothala mus	8 ♂	B	T	60 %	-	400
PARACHLOROPHENYLALANINE										
Blum K Geller I 1969					♂	B				
Margules D L 1969	316	i p	-15	dorsal nucleus of raphé	6 ♂	B	120 200	100 pps	0 2	150
Black, W C Cooper, B R 1970	3x300 24-hr in terval	or	+16 hrs	lat hypothalamus (MFB)	7 ♂	B	300	200 pps	0 2	250
Gibson S et al 1970	150 200	i p	-	post hypothalamus (MFB)	13 ♂	B	5 14 V	60 %	-	150
Stark P et al 1970	350	i p	1 and -6 hrs	post hypothalamus	6 ♂	B	T	60 %	-	250
Cooper B R et al 1971	3x300 24-hr in-terval	or	-5 hrs	septal (6) lat hypothalamus (6)	12 ♂	B	300	200 pps	0 2	250
Poschel B P A Ninteman F W 1971	500	i p		MFB ventral tegm subst nigra dorso-med hypothalamus ret form	14 ♂	M	10-15	60 %		400
Stark P Fuller R W 1972	350	i p	-1 hr	post hypothalamus	6 ♂	B	T T+1, T+2	60 %	-	250

SESSION		RESULTS	REMARKS
Dur. min	Proc.		
60	CRF	- No effect at .0625-1.0 mg/kg. - Slight ↓ at 1.5 mg/kg. - Severe ↓ at 2.0 mg/kg.	1 mg/kg and > hind limb paralysis. 2.0 mg/kg convulsions.
265	CRF	- Prior treatment with 25 mg/kg with pargyline 1 day before test required. - ↗, onset 45 min after injection. - At 20 mg/kg toxic.	Cumulative records of representative rats.
	CRF	- In 5/7 rats mild ↓ after Ro 4-4602 for ± 40 %.	Cumulative record.
90	CRF	- ↓, onset 10 min after injection - % change with 28 mg/kg 32 %, with 57 mg/kg. ± 57 %, with 115 mg/kg ± 66 %. - Peak depression 84 % between 20 and 30 min after administration. - With higher doses 50 % ↓, 90 min after injection.	Biochemical determinations of content of biogenic amines.
	CRF	↗ persisted > 3 days	No details.
45	CRF	- ↓ from 528 mean control response rates/8 min, to 472 ($p < .05$). - Recovered at 24 hrs.	
2x30	F.I. 1 5 sec	16 hrs after last injection no effect on either of the 2 measures	30-min lever pressing, 30-min rate-free, 10-min interval.
2-min periods	CRF	Drug-effect measured in changes of control threshold (increase + 1.1 V, +2.2 V, +3.3 V). 9 rats ↗, 3 no effect, 3 ↓ threshold, 2-3 days after injection.	5-HT ↓ 48 % and 30 % of control.
		- At 6 hrs 50 % ↓ at threshold current. - At 24 hrs 19 % ↓ (not significant). - No significant effects of suprathreshold self-stimulation.	Serotonin still ↓ to 79 %.
2x20		- No significant main drug effect or drug interactions	Rate-free situation. 10-min interval.
		Test 3, 7 and 14 days after drug treatment % change. 3 days after injection: - ↗ in MFB and ventral tegmental area of Tsai, - small ↗ or no effect in substantia nigra and MFB (anterior), - no effect in dorsomedial hypothalamus, - ↓ in reticular formation	
4x5		- Threshold ↗ = responding ↓ - Maximum effect at 6 hrs. - No effect on suprathreshold intensities	T = threshold +1 - +5 μA, no correlation with 5-HT

2. DISCUSSION

2.1. Methodology

Most authors used the intraperitoneal **route of drug administration,** by which solutions as well as suspensions can reliably be applied. Drug-effects can differ according to the injection route, as regards local effects, uptake in blood, distribution, etc. For example cocaine injected i.p. causes stereotype behaviour at dose levels much lower than when given s.c. (Simon et al., 1972). Consequently, cocaine might elicit a different effect on operant behaviour according to the administration route. In several studies only a single **dose** is used. This way of studying drug-effects is not justified because the shape of the dose-response curves may differ from drug to drug. Moreover, the shape of the response curves may depend upon the particular test used (see effects of narcotic analgesics, Wauquier and Niemegeers, 1976a). The **period** of measurement after drug-injection can be an important variable, as shown, for instance, in the study of Adams et al. (1972). Morphine causes response depression when self-stimulation is measured for 2 hours following injection; however, responding is significantly increased 5 to 6 hrs after injection. We showed that the response depression or facilitation found with CNS-stimulants depends to a large extent on the period of measurement (Wauquier and Niemegeers, 1974b).

In all the studies, regardless of whether sine-wave **current** or square wave pulses were used, the variations of the base-line were produced by changing the intensity of the current. Low base-line rates are mostly obtained by applying «threshold» currents. The definition of threshold is often very arbitrary and vague. Furthermore, as will be shown in our experiments, the use of low frequency stimulation results in poor responding which is very sensitive to drugs. Drug-effects can differ according to the **base-line** rates of responding (see for example the effects of CNS-stimulants, Wauquier and Niemegeers, 1974b). Practically all authors studied drug-effects using a continuous reinforcement (CRF) **schedule.** Interpretation of data has to take into account the particular schedule used. For example: neuroleptics effectively decrease the response rate on a high fixed ratio schedule (i.e. with little reinforcement), whereas their inhibitory effect is less pronounced on a CRF-schedule.

Most of the studies have been carried out on rats lever-pressing for hypothalamic stimulation. Drug-effects may also depend on the **site of stimulation** (see for example: Phillips and Fibiger, 1973).

From a methodological point of view the following points should therefore be considered: the injection route; the dose; the stimulation parameters; the base-line; the schedule; the injection time; the implantation site. These and other situational or experimental variables make a comparative study on drug-effects extremely difficult.

2.2. Drug-analyses

Different publications provide descriptive analyses and contain statements which lack **quantitative** accuracy. A frequent failure is the description of results by showing the results of a «representative animal». This way of presenting data is illustrative but facilitates erroneous generalization about drug-effects. Otherwise there is a lack of **qualitative** observations relevant to the interpretation or description of the results obtained. A drug-effect might be essentially unrelated to the behaviour studied (e.g. barbiturates depress self-stimulation because barbiturate-treated rats are drowsy or sleep; they are, therefore, unable to press a lever).

For comparative purposes it would be worthwhile relating the drug-effects obtained on self-stimulation to those obtained on other **operant behaviours** and/or to the results obtained in other pharmacological or biochemical tests. Such comparisons might indicate whether the modification of self-stimulation behaviour would permit generalized conclusions. It therefore should be emphasized that the effects obtained on self-stimulation behaviour should be analyzed quantitatively and should be related to qualitative observations as well as to effects obtained in other tests. Such an analysis may enable one to differentiate specific from unspecific drug effects.

2.3. Theoretical aspects

Some theories of psychic diseases are derived from theoretical concepts related to self-stimulation behaviour. Yet the heuristic value of these theories has not been subjected to experimental verification. For example, Stein (1967) proposed that depression could be caused by a hypoactive reward system or by an overactive punishment system. A valid model of depression using self-stimulation behaviour, would be one in which mood-elevating drugs, such as the tricyclic antidepressants, induce behavioural facilitation. Such a model has not yet been developed. It is interesting, however, that in a situation in which a progressive fixed-ratio schedule was used, i.e. in which reinforcement required progressively more and more effort, antidepressants enhanced responding which normally dropped gradually to zero (unpublished observations). There are few studies dealing with the interaction of drugs which might elucidate or confirm suspected interactions between brain systems (e.g. Wauquier and Niemegeers, 1975; Wauquier et al., 1975).

It is obvious that drugs may affect self-stimulation behaviour by an action on a large number of systems, amongst others: the motor system, the sensory system, the integrative sensory-motor system and the reinforcement system. Drugs may also interfere with stimulation-induced or situation-dependent behavioural patterns. It will therefore be extremely difficult to affect differentially the various systems involved in behaviour.

IV. General methods

1. SUBJECTS

Adult male Wistar rats from the Janssen breeding laboratory, weighing 250 ± 10 g at the time of surgery were used. They were transferred to the laboratory in which environmental conditions were kept constant, i.e. temperature of 21 ± 1°C, relative humidity of 65 ± 5 %. A normal light (12 hrs) - dark (12 hrs) cycle was used and rats were tested during daytime (light-period). The rats were kept in individual cages and provided with food and water ad libitum, except during the experimental sessions. When the oral route of drug administration was used, rats were deprived of food for a period of 24 hours prior to the experimental session.

2. SURGERY

Rats were anaesthetized with Thalamonal (1) (0.5 ml/kg s.c.) and positioned in a David Kopf Stereotaxic instrument with rat adaptor. The tooth bar was placed 5 mm above the ear bars. A sagittal incision was made on the skin of the skull, the membranes covering the skull were cut away and the skull surface was made clean, so that the external landmarks became clearly visible. The bregma was taken as reference point and with the use of coordinates adapted from the stereotaxic atlas of König and Klippel (1963) the site at which the electrode had to be placed was marked. Four holes were then drilled in the skull using a dental drill: one where the electrode entered the brain and three others into which jeweller's screws were driven. One of the screws served as an indifferent electrode and was placed anterior to the bregma, the other two served as anchor points for the dental cement covering the contact points after the electrode has been put into position. Coordinates for electrode placement in the lateral hypothalamus of the MFB were: anterior 4.0 mm, lateral 1.4 mm and 3.0 mm above the zero stereotaxic point, according to the atlas; and actual coordinates: 1.2 mm posterior to the bregma, 1.4 mm lateral and 8.8 mm beneath the surface of the skull.
All studies involved stimulation via a monopolar electrode. However, a bipolar electrode was implanted in such a way that two monopolar electrodes could be used in the same rat. The electrodes consisted of 0.254 mm nichrome wires twisted together, insulated at all points except for the cross section of the tip.

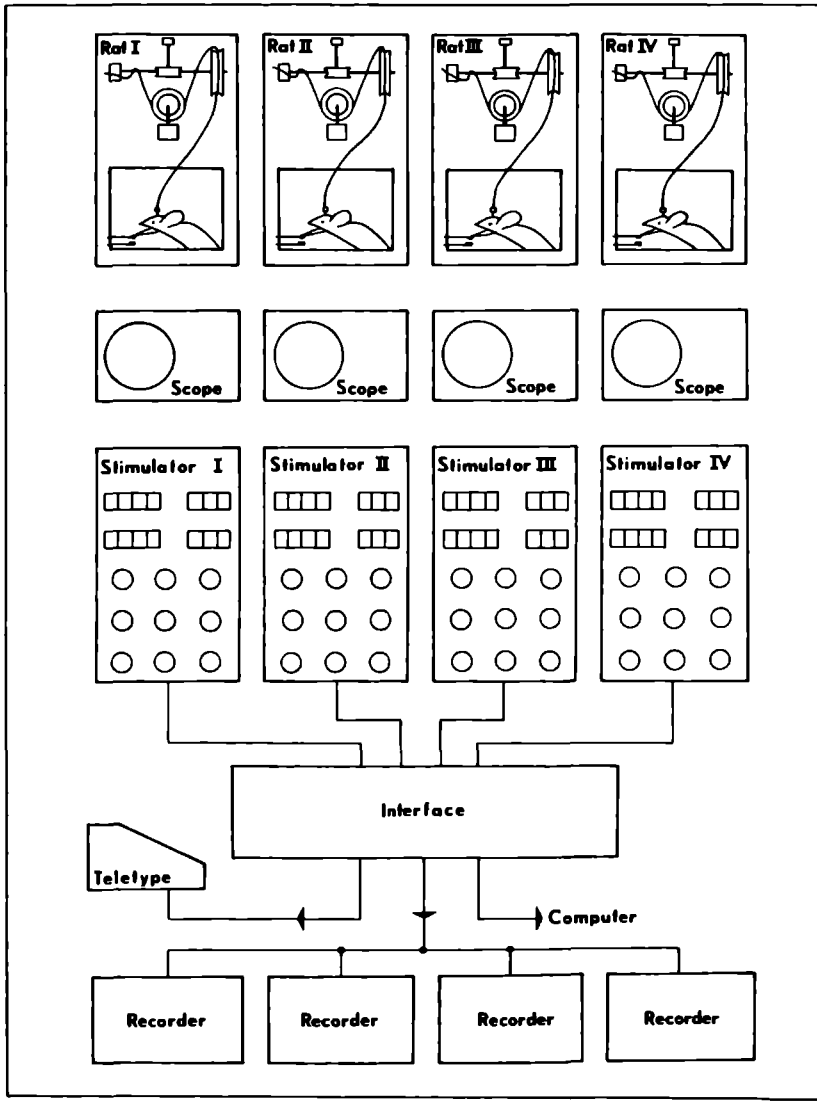
(1) Thalamonal®: droperidol 2.5 mg and fentanyl citrate 0.0785 mg per ml.

After implantation, rats were given 3 mg of nalorphine HCl i.v. in order to accelerate recovery from anaesthesia. Thereafter they were transferred to their home cage. The experiments started at least one week after surgery.

3. MATERIALS

Fig. 1 is a schematic diagram of the general set-up.

Fig. 1: General set-up.



3.1. Cage

The experimental compartment was a 20 cm wide, 25 cm long and 33 cm deep PVC (polivinylchloride) cage with a 6 x 3 cm stainless steel lever mounted in the back wall of the cage, 6 cm above the floor, which was made of stainless steel grid. Underneath was a funnel collecting faeces and urine separately. The front wall of the cage was made of transparent perspex, allowing direct observation of the rat. To prevent twisting of the electrode leads, a modification of Berkley and Kling's mercury contact swivel device with vertical movement compensation (Berkley and Kling, 1967) was constructed.

3.2. Electrode

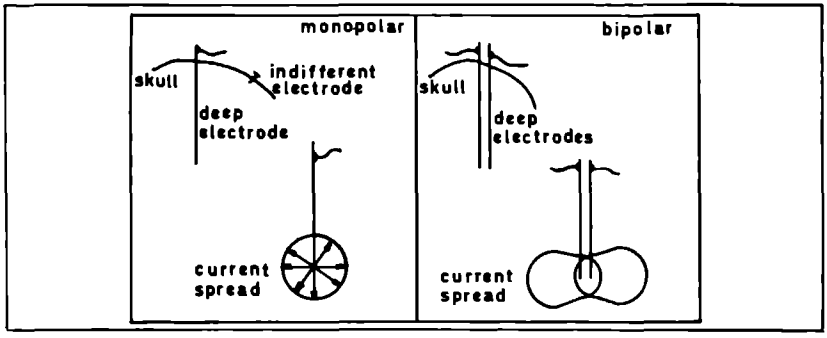
3.2.1. Metal

In most studies stainless steel or platinum electrodes were used. Nichrome electrodes are generally used less as there is a lack of information about histological changes after chronic stimulation.
There are impedance changes related to the type of electrode used, particularly with stainless steel electrodes. Moreover, mental deposits can be detected. Bollinger and Gerall (1971) and Wetzel et al. (1969) concluded in their comparative study that platinum electrodes resulted in a more stable self-stimulation rate together with a constant impedance. In our studies nichrome electrodes were used. Impedance was measured over periods of up to several months. As with other electrodes transient impedance changes could be detected, but there was no evidence of progressive changes (gradually increasing) during chronic experiments. Histological verification showed gliosis of tissue but no evidence of metal deposits was found.

3.2.2. Monopolar vs. bipolar stimulation

Bipolar stimulation is current given between the points of 2 electrodes inserted into the brain. With monopolar stimulation one electrode is implanted in the brain, while the second one is placed on the skull or in the skin (usually of the neck). The latter electrode is an «indifferent», i.e. this electrode does not determine the direction of the current (Fig. 2). Theoretically this electrode should be placed at infinity.

Fig. 2: Monopolar and bipolar electrode.



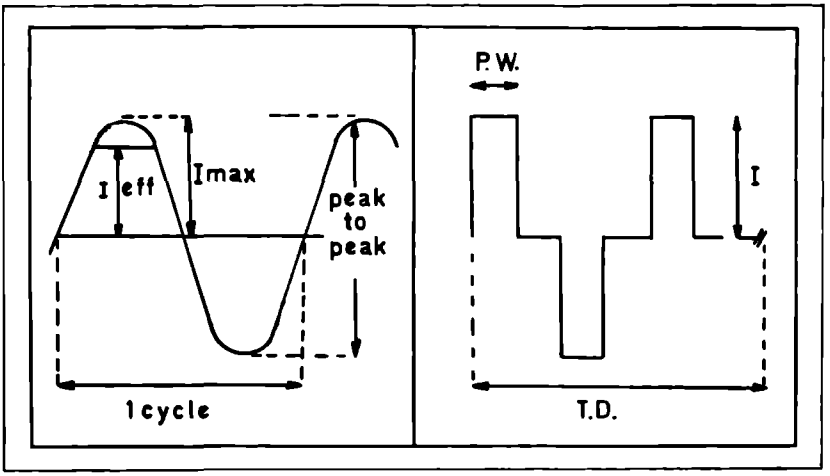
The position of the (deep) electrode in relation to the stimulated structure(s) is of primary importance. It is, however, experimentally difficult to measure and compare the distribution of the current (and density in the field), when monopolar or bipolar electrode stimulation is used. Theoretically it is possible to make some statements but these are based on a number of assumptions which are not borne out in brain-stimulation (Stark et al., 1962). Only indirect evidence can be obtained and the stimulated structure is often very heterogenous.
Most of the authors used bipolar stimulation on the logical assumption that monopolar stimulation involves a greater neuronal field. It is, however, important to consider the many different stimulation parameters used. Current distribution will be pronounced if high intensities are used, even with bipolar electrodes. General statements must await comparative studies on current distribution using a large number of different stimulus parameter combinations. Of importance is the fact that manipulation of these combinations is found to activate a particular set of fibres responsible for the behaviour observed. Even with monopolar electrodes these fibres are very close to the point of the electrode (within a range of 1/4 to 1/2 mm, for stimulation-induced eating behaviour, Wise, 1972).

3.3. Stimulator and electrical parameters

3.3.1. Considerations on wave-form and current-characteristics

In the study of behaviour induced by electrical current, 2 wave-forms are mainly used: sinusoidal and square wave or rectangular pulses (monophasic and biphasic). They are illustrated in Fig. 3. The different stimulation parameters are also indicated.
In a short review on self-stimulation data, Wetzel (1968) mentioned that approximately fifty percent of the authors (150 publications surveyed) used sine-wave current (50 or 60 Hz). Very few authors compared the effectiveness of sine-wave current with square wave or rectangular pulse wave (Su et al., 1966). No conclusive reasons can be found for the selection of one or the other wave-form (such as showing, for example, that one of the wave-forms used is more physiological than the other). Preference for square wave pulse current is mainly based on practical advantages: more individual parameters can be manipulated. Because of the possibility of varying the interpulse-interval (or frequency) it is possible to study refractory periods of a population of neurons involved in the stimulation (e.g. Deutsch, 1964; Smith and Coons, 1970; Wetzel, 1972).
Monophasic cathodal stimulation (one side rectangular pulses with negative pulse polarity) is quite common in neurophysiological research. Lilly started a series of studies using a wave-form which «did not destroy brain tissue» (biphasic triangle wave-form) (Lilly et al., 1955). However, according to different authors even the use of monophasic stimulation does not result in brain lesions (e.g. Wetzel et al., 1969).
A progressive distortion of the signal (as seen on the oscilloscope) and a decrease in pulse amplitude constitute electrical evidence of tissue

Fig. 3: Electrical wave-forms: ***left side:*** *sinus wave,* ***right side:*** *biphasic rectangular pulses or square wave.*



Amplitude of intensity (I):
I max. = 1.41 I effective

$$I\,eff. = \sqrt{\frac{I^2\,max}{2}} = \frac{I\,max}{\sqrt{2}}$$

$$= 0.707\ I\ max$$

Frequency (F): expressed in cycles/second

$$f = \frac{1}{T}$$

I: intensity (in milli Ampères or micro Ampères)
F: frequency (pulses per sec)
P.W.: pulse width (millisec)
T.D.: train duration (millisec)
Q: quantity of charge (Coulomb) = A x sec

changes. A distortion of rectangular pulses given by a constant current source is, however, observed immediately. This is due to impedance changes (vide infra). Tissue injury is found by histological examination, showing gliosis, debris of pigmented particles and, depending on the electrode used, metallic deposits.

It seems safer to use biphasic square wave pulses in order to reduce the possibility of injury to brain tissue, especially in chronic experiments.

The effects of the stimulation depend to a large extent on the current used. The effective intensity of the current applied to the brain depends on the resistance of the rat (connected in series with the circuit), on the resistance of the electrode and on the mechanical connections. The total of the different resistances or impedance (Z) is expressed by the formula Z = E (voltage)/I (intensity).

Polarization impedance of the contact surface between the electrode and the brain tissue, and the impedance of the brain tissue itself are components which change the total impedance.

The impedance can change during the experiment. The increase of impedance during the very first minutes of the experiment is a

phenomenon observed regularly. This increase can be due to certain changes of the electrolytes at the tip of the electrode or to glia cell accumulation (Bollinger and Gerall, 1971). Impedance increase associated with a decrease of self-stimulation rate can be found during long-term experiments. An increase of impedance and a decrease of current was associated with a decrease in lever-pressing when a constant voltage source was used (Bollinger and Gerall, 1971). The long-term change is ascribed to lesions produced by prolonged stimulation, or is due to the displacement by ionic current of charged particles. Therefore it is advisable to use a constant current source which delivers a stabilized current intensity in the stimulated tissue.
In our experiments it was found that with a constant current source brain-stimulation could be maintained over long periods, without the necessity of adjusting the current. Impedance changes were not detected except shortly before rats completely stopped self-stimulation behaviour. These, however, occurred only after extended periods (up to many months of experiment) and could be due to lesions.

3.3.2. Stimulator and recording

Electrical stimulation was given by a stimulator of our own construction (Geivers et al., 1973, 1975) with constant current output from an integrated circuit. The rats could obtain electrical stimulation by pressing on a lever. The trains of biphasic rectangular pulses elicited were adjustable for constant current intensity, pulse frequency, pulse width and train duration. Fixed ratio schedules (ratio of the number of stimulations to the number of responses) could be programmed; an inhibition circuit prevented the responses given during the stimulation train from being rewarded. The output of the stimulators was monitored on an oscilloscope and the amplitude of the constant current measured across 1 Ω. The voltage from oscilloscope readings over the current input provided the impedance. The number of responses (number of lever-pressings) and the number of stimulations received were visualized by seven segment displays. The numeric indicators were driven via Binary Decimal Code (BCD) and converted in the interface unit to American Standard Code for Information Interchange (ASCII-code). The information from the stimulators was changed in interface units from parallel to serial. The interface unit drove the teletype, which collected every minute the number of lever-pressings given and the number of stimuli applied. The numbers of responses and stimuli from each stimulator were converted via a digital to an analogue voltage which controlled a pen recorder. The responses and stimuli were recorded separately.

4. ESTABLISHMENT OF SELF-STIMULATION

Rats put in a self-stimulation cage show the characteristic behavioural pattern common to all rats in a new environmental situation. With priming stimuli (i.e. brain-stimulation delivered by the investigator), rats either approach, escape or act neutrally. When approach behaviour is

observed, which consists of a detailed exploration of the nearby surroundings, the investigator usually gives priming stimuli when the rat approaches the lever. Very soon the rat discovers that pressing the lever elicits brain-stimulation and in turn, brain-stimulation reinforces the lever-pressing. Self-stimulation behaviour is therefore quickly established, but not in all implanted rats and with various degrees of response.

A total of 500 rats implanted with electrodes in the medial forebrain bundle region (MFB) of the lateral hypothalamus, were sampled. They were all trained in half-hour sessions for at least 4 days. In 46.4 % of the rats brain-stimulation applied by the investigator elicited escape behaviour (9.4 %) or induced motor effects (circling, tremor, shivering etc., 37.0 %); in 53.6 % self-stimulation behaviour could be established: in 17.4 % low lever-pressing (100-300 responses), in 21.2 % intermediate response rates (300-800) and in 15.0 % high self-stimulation response rates ( ) 800) were found.

The fact that in 46.4 percent of the rats, it was not possible to induce self-stimulation behaviour, may be due to a variety of reasons. Obviously some electrodes failed to reach the target structure. This may be due to anatomical differences from rat to rat, to incorrect positioning of the rat in the stereotaxic instrument, etc.

Histological monitoring enables us to pick out the rats which have incorrectly implanted electrodes. In the nearby surroundings of the lateral hypothalamus, however, self-stimulation may be found, for example, in the zona incerta, Forel's Field 2, medial to the lateral hypothalamus, dorsal to the fornix and in the capsula interna. On the other hand there are some unidentified reasons why rats failed to show self-stimulating reactions to electrical stimulation via electrodes which histological examination revealed to have been correctly implanted.

Within the group of correctly implanted rats, the number of self-stimulation responses can differ greatly. Histological monitoring does not always distinguish between groups which differ in their total response output.

An obvious reason responsible for the inter-individual variability in rate of lever-pressings is the fact that self-stimulation is elicited through stimulation of a field of neurons. Furthermore, relatively large electrodes are necessary (seemingly a minimum of 80 μmm in diameter). The stimulated structure, particularly the lateral hypothalamic region, is very heterogeneous, containing fibres of different sizes, ascending and descending axons and cell bodies.

It is conceivable that, within a particular region, different fibres are involved in the stimulation fields of different rats. This will be dependent, for example, on the relative position of the 2 electrodes of a bipolar set (Szabó and Milner, 1972) or on the position of the insulate-free tip of the electrode in relation to the stimulated structure(s) (orientation of the electrode) (Szabó et al., 1972).

A final word concerns intra-individual variability of self-stimulation. As will be described further (see Chapter VI. 2.) self-stimulation could be maintained over long periods of time. There was a general tendency to a progressively decreasing responding over time, which was, however, not observed in all rats.

V. The influence of various stimulus parameter combinations

Although the literature on lever-pressing for intracranial stimulation is extensive, only a few studies deal systematically with the influence of parameters of electrical stimulation on response rate.
Stimulation with a single pulse cannot induce self-stimulation behaviour. This fact recalls the results of experiments of Brookhart (1952) who found that stimulation of the bulbar pyramidal tract with few pulses also fails to induce muscle contraction. Most of the earlier studies on electrical self-stimulation used sine-wave current with a frequency of 50 Hz. The self-stimulation rate was therefore mainly varied by changing the intensity. In the various studies intensities ranged from a few micro Ampères (e.g. Uyeda and Genegerelli, 1959) up to 50 milli Ampères (e.g. Stein and Ray, 1960).
Using rectangular pulses, different authors studied the effects of varying the frequency, pulse width and train duration of electrical stimulation on the rate of lever-pressing. Frequencies ranged from 20 pulses per second (pps) (Gengerelli et al., 1963; Keesey, 1962) to 480 pps (Beyra and Voisin, 1971; Elder and Work, 1965), pulse widths from 50 μsec (Stein and Ray, 1960) to 5 msec (Ward, 1959) and train durations from 0.03 sec (Beyra et al., 1969a, b) to 10 sec (Hodos, 1965). In the case of sine-wave current, frequencies ranged from 10 to 3000 cycles per second (Ridgway et al., 1965; Uyeda and Gengerelli, 1959).
These studies clearly show that a large variety of stimulus parameters is able to elicit self-stimulation behaviour. Several authors hypothesize that a common variable underlies the influence of the different stimulus parameters: the quantity of charge (i.e. the total quantity of electricity provided by the combination of the different stimulus parameters). In our investigation, we tried to find an answer to the following questions:

1. Is response rate dependent upon quantity of charge?
2. What is the relationship between the variation of different stimulus parameters and the amount of lever-pressing?
3. Is it possible to predict the response rate elicited by different stimulus parameter combinations?

1. EXCITABILITY OF THE NEURONAL TISSUE WITH RESPECT TO SELF-STIMULATION

The excitability of peripheral nerves has been documented by many authors (e.g. Katz, 1939). The classical strength-duration curve demonstrates the limits of neuronal excitability: a stimulus has to exceed an

intensity-threshold in order to induce a nerve-impulse (rheobase); a certain pulse duration is necessary.
Therefore a certain quantity of charge (Q) is necessary to induce a nerve impulse. The threshold was found to be between 0.2 and 0.5 μC for cortical electrodes and 0.05 μC for deeper placements (Lilly, 1961). There are several reasons why classical strength-duration curves can hardly be applied directly to self-stimulation experiments where behaviour is the dependent variable.

a. A single nerve responds to an all-or-none law, in that an axon is stimulated when the intensity of the pulse exceeds a threshold intensity. Behavioural effects in general require the firing of many neurons close to the electrode tip. Stimulation with pulse pairs, in which the interval between each pair of pulses is varied, can be used to characterize the refractory period of a population of neurons. These neurons may have different diameters and hence different refractory periods (e.g. Rolls, 1973).
Single pulse stimulation is, however, insufficient to induce self-stimulation behaviour. This clearly demonstrates that temporal summation is required and that reinforcement of behaviour, to some extent, depends upon the degree of transsynaptic activation (Gengerelli et al., 1963).

b. A definition of «threshold» in self-stimulation requires a behavioural criterion, for example, the amount of lever-pressing. Threshold detection requires complicated procedures (Huston and Mills, 1971).

c. The stimulation occurs in a neuron pole, i.e. transmission in a volume conductor. Recording in the neuron pole stimulated reveals a complex process of neuronal excitatory and inhibitory activity (Ito, 1972).

Self-stimulation behaviour is induced by the stimulation of a set of neurons, producing organized patterns of cellular excitation (Mickle, 1961). First, there is spatial summation in the stimulation field, which is very heterogeneous in the lateral hypothalamus, because this neuroanatomical structure contains fibres which have different threshold values (Szabo and Lénard, 1974). Second, temporal summation of neurons around the tip of the electrode and at points further away occurs. Increasing the intensity of the stimulation will increase the stimulation field and increasing the pulse width will not enlarge the distribution because of volume conduction, but will depolarize neurons at the periphery above the threshold («fringe cells», Abeles, 1967a, b). It is important to note that an increase of train duration will increase transsynaptic activity remote from the stimulation point (Gengerelli et al., 1963).
Studies on the refractory period in self-stimulation have been conducted by different authors using behavioural criteria (Kestenbaum et al., 1973; Wetzel, 1971). An interpulse-interval of 1 msec was found necessary to sustain self-stimulation behaviour.
The neuronal activity recorded close to the stimulating electrode is, how-

ever, not always excitatory. Ito (1972), for instance, showed that rewarding brain-stimulation inhibited neurons in the lateral hypothalamus at a distance of 1 to 2 mm from the stimulating electrode in the same area. When the pulse trains were repeated these inhibitions decreased and excitatory responses became apparent. Further, Olds (1973) showed that lateral hypothalamic neurons showed either pure inhibition or an activation-inhibition sequence in response to medial forebrain bundle stimulation. These findings pose the question of whether the suppression of neuronal firing is related to brain-reward (as hypothesized by Olds, 1973).

The above considerations demonstrate the importance of studying self-stimulation behaviour induced by various combinations of stimulus parameters. In analogy with peripheral nerve activity it could be argued that the interaction of the different stimulus parameters expressed by the total electrical activity contained in one stimulation was the determinative factor.

2. EXPERIMENTAL STUDY (1)

2.1. Experimental procedures

Training

Rats were implanted with a monopolar electrode in the lateral hypothalamic area of the medial forebrain bundle.

One week after the operation, the rats were trained to press the lever on a continuous reinforcement schedule 1:1, ten minutes a day for three to six days. Then the rats were given a fixed ratio reinforcement schedule 2:1 with T-inhibition (2 responses were needed in order to obtain one stimulus and responses occurring during the stimulus-train were not rewarded) and further trained in sessions of 4 x 10 minutes, each 10 minute period being separated by 1 minute extinction during which no stimulation was delivered. The stimulus parameters during training were kept constant and the training was continued until the rats had adapted to the procedure (usually 2 weeks).

Testing

Five separate experiments were performed. Each experiment started with 4 rats, lasted 4 weeks, and included 4 sessions a week. Each session consisted of 4 ten-minute periods of a fixed ratio schedule 2:1 with T-inhibition, followed by 1 minute extinction. Table 1 shows the detailed sequence of the different stimulus parameters in each experiment and within the sessions. At the end of the experiments, the brains were successively perfused with saline and with 10 % formalin. The electrodes were then localized in serial 4 μ sections stained with luxol fast blue.

(1) This study was published earlier. Wauquier, A., Niemegeers, C.J E , Geivers, H A.: Intracranial self-stimulation in rats as a function of various stimulus parameters I. An empirical study with monopolar electrodes in the medial forebrain bundle Psychopharmacologia 23, 238-260 (1972).

Table 1: Sequence of the various stimulus parameters for the individual rats in the 16 experimental sessions.

Exp. No.		1-2				3				4-5			
Rat No		1, 5	2, 6	3, 7	4, 8	9	10	11	12	13, 17	14, 18	15, 19	16, 20
Weeks	Session	Periods 1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4
1+4*	1	AAAA	BBBB	CCCC	DDDD	D_{1111}	D_{2222}	D_{3333}	D_{4444}	A_{1234}	B_{1234}	C_{1234}	D_{1234}
	2	BBBB	DDDD	AAAA	CCCC	D_{2222}	D_{4444}	D_{1111}	D_{3333}	A_{2413}	B_{2413}	C_{2413}	D_{2413}
	3	CCCC	AAAA	DDDD	BBBB	D_{3333}	D_{1111}	D_{2222}	D_{2222}	A_{3142}	B_{3142}	C_{3142}	D_{3142}
	4	DDDD	CCCC	BBBB	AAAA	D_{4444}	D_{3333}	D_{2222}	D_{1111}	A_{4321}	B_{4321}	C_{4321}	D_{4321}
2	1	ABCD	ABCD	ABCD	ABCD	D_{1234}	D_{1234}	D_{1234}	D_{1234}	B_{1234}	D_{1234}	A_{1234}	C_{1234}
	2	BDAC	BDAC	BDAC	BDAC	D_{2413}	D_{2413}	D_{2413}	D_{2413}	B_{2413}	D_{2413}	A_{2413}	C_{2413}
	3	CADB	CADB	CADB	CADB	D_{3142}	D_{3142}	D_{3142}	D_{3142}	B_{3142}	D_{3142}	A_{3142}	C_{3142}
	4	DCBA	DCBA	DCBA	DCBA	D_{4321}	D_{4321}	D_{4321}	D_{4321}	B_{4321}	D_{4321}	A_{4321}	C_{4321}
3	1	DCBA	DCBA	DCBA	DCBA	D_{4321}	D_{4321}	D_{4321}	D_{4321}	C_{1234}	A_{1234}	D_{1234}	B_{1234}
	2	CADB	CADB	CADB	CADB	D_{3142}	D_{3142}	D_{3142}	D_{3142}	C_{2413}	A_{2413}	D_{2413}	B_{2413}
	3	BDAC	BDAC	BDAC	BDAC	D_{2413}	D_{2413}	D_{2413}	D_{2413}	C_{3142}	A_{3142}	D_{3142}	B_{3142}
	4	ABCD	ABCD	ABCD	ABCD	D_{1234}	D_{1234}	D_{1234}	D_{1234}	C_{4321}	A_{4321}	D_{4321}	B_{4321}
									Week 4	D_{1234}	C_{1234}	B_{1234}	A_{1234}
										D_{2413}	C_{2413}	B_{2413}	A_{2413}
										D_{3142}	C_{3142}	B_{3142}	A_{2142}
										D_{4321}	C_{4321}	B_{4321}	A_{4321}

Different systematically varied parameters, in brackets symbols used.
Exp. 1, 2, 4, 5 pulse intensities in mA 0 100 (A), 0 150 (B), 0 200 (C), 0. 250 (D)
Exp 3 pulse width in ms 2 (1), 4 (2), 6 (3), 8 (4).
Exp 4 pulse frequency in pps 20 (1), 40 (2), 60 (3), 80 (4).
Exp 5 : train duration in ms 200 (1), 400 (2), 600 (3), 800 (4).

* 1+4 experiments 1, 2 and 3 only

2.2. Results

Experiment 1. (1) The detailed individual response rates obtained with various pulse intensities at a constant charge of 50 μC per stimulation and the corresponding pulse frequency, pulse width, and train duration are indicated in Table 2. As the electrode broke off, rat 1 did not perform the complete experiment, and was not considered for evaluation.
The total number of responses given by the three rats was 73518, the total number of stimuli received 33253, i.e. a mean of 2.21 responses per stimulus. The individual differences in response rate varied from 9006 to 45193 (Fig. 3).
The response rate was lowest during the last week, i.e. 4060 (rat 2), 1369 (rat 3) and 9418 (rat 4), although the response rate did not gradually decrease from the first to the last week.
The total and individual response rates increased with increasing pulse intensities (Fig. 1).
The response rate gradually decreased during the four periods within each session at .100 mA, .150 mA and .200 mA intensities but remained approximately constant at the intensity of .250 mA (Fig. 2).

Experiment 2. (1) The detailed individual response rates obtained with various pulse intensities at a constant charge of 25 μC per stimulation and corresponding pulse frequency, pulse width, and train duration are indicated in Table 3. Rat 7 was not considered for evaluation, as from the second week its responses dropped to zero.
The total number of responses given by the three rats was 75832, the total number of stimuli received 34678, i.e. a mean of 2.19 responses per stimulus. The individual differences in response rate varied from 17987 to 36556 (Fig. 3).
The response rate was highest the second week for rat 6 (9955) and the third week for rats 5 (5379) and 8 (6551). The response rate was lowest the first week for rats 5 (3119) and 8 (3448), the last week for rat 6 (7654).
The total and individual response rates became higher as intensities increased from .100 mA to .200 mA but sharply decreased at the intensity of .250 mA (Fig. 1).
The response rate decreased during the four periods within each session at .100 mA, .150 mA and .250 mA intensities, and remained approximately constant at the intensity of .200 mA (Fig. 2).

Experiment 3. (2) The detailed individual response rates obtained with various pulse widths at a constant intensity, frequency and train duration and corresponding quantities of charge are indicated in Table 4. Rat 9 was not considered for evaluation as, from the third week, the responses dropped to zero.
The total number of responses given by the three rats was 139895, the

(1) Stimulus parameters during training: pulse intensity: .200 mA, pulse frequency: 50 pps; pulse width: 10 ms; train duration 500 ms.

(2) Stimulus parameters during training. pulse intensity: .200 to .250 mA; pulse frequency. 50 pps; pulse width. 10 ms; train duration: 500 ms.

Table 2: *Experiment 1. Variation of pulse intensity at a constant charge of 50 µC per stimulation. Number of responses for 3 trained rats in 16 experimental sessions (4 per week for 4 consecutive weeks). Each session (SES) was divided into 4 periods (PER) of 10 minutes stimulation followed by 1 minute extinction.*

Stimulus parameters[a]				SES	PER	Rat No. 2				Rat No. 3				Rat No. 4				Rat No.		
						Weeks				Weeks				Weeks				2	3	4
INT. mA[b]	FREQ. pps[c]	P. W. ms[d]	T. D. ms[d]			1	2	3	4	1	2	3	4	1	2	3	4	Σ of 4 periods		
.100	80 (Q 48.0 µC)	10	600	1	1	84	29	26	21	67	38	44	40	524	781	369	319	160	189	1993
					2	40	27	12	4	5	28	15	3	164	80	97	91	83	51	432
					3	5	11	6	3	7	26	2	39	59	80	24	51	25	74	214
					4	6	6	7	1	0	1	3	3	53	49	57	16	20	10	175
																		288	324	2814
.150	66 (Q = 49.5 µC)	10	500	2	1	343	224	60	43	79	58	300	109	1046	1105	1115	1128	670	546	4394
					2	149	74	12	9	42	10	22	37	946	1129	1168	326	244	111	3569
					3	31	7	15	12	12	9	5	69	356	158	893	200	65	95	1597
					4	50	19	7	0	65	0	4	6	483	257	457	114	76	75	1311
																		1055	827	10871
.200	50 (Q = 50.0 µC)	10	500	3	1	630	628	684	667	675	469	495	196	1083	1144	1092	1160	2609	1835	4479
					2	301	263	440	53	560	145	48	81	768	1105	958	539	1057	834	3370
					3	30	628	30	21	25	16	82	57	258	838	1026	291	709	180	2413
					4	16	260	4	32	37	11	27	28	159	602	1068	422	312	103	2251
																		4687	2952	12513
.250	80 (Q = 50.0 µC)	5	500	4	1	843	737	678	668	724	593	303	395	1062	1075	1083	1113	2926	2015	4333
					2	922	923	876	865	147	438	169	198	1152	1209	1294	1210	3586	952	4865
					3	810	880	918	892	86	573	227	90	1168	1282	1246	1257	3500	976	4953
					4	814	912	782	769	137	467	338	18	1153	1217	1275	1181	3271	960	4826
																		13283	4903	18977
.100 mA						135	73	51	29	79	96	64	85	800	990	547	477			
.150 mA						573	324	94	64	198	77	331	221	2831	2649	3641	1768			
.200 mA						977	1779	1158	773	1297	641	652	362	2268	3689	4144	2412			
.250 mA						3389	3452	3254	3194	1094	2071	1037	701	4535	4783	4898	4761			
Per week						5074	5628	4557	4060	2668	2885	2084	1369	10434	12111	13230	9418			
Total responses						19319				9006				45193						

[a] INT. pulse intensity, FREQ. pulse frequency, P. W. pulse width, T. D. train duration, Q. = quantity of charge per stimulus
[b] mA milli Ampere
[c] pps pulses per second
[d] ms milliseconds

Table 3: *Experiment 2. Variation of pulse intensity at a constant charge of 25 μC per stimulation. Number of responses for 3 trained rats in 16 experimental sessions (4 per week for 4 consecutive weeks). Each session (SES) was divided into 4 periods (PER) of 10 minutes stimulation followed by 1 minute extinction.*

Stimulus parameters[a]				SES	PER	Rat No. 5				Rat No. 6				Rat No. 8				Rat No		
INT[b] mA	FREQ. pps[c]	P W ms[d]	T D ms[d]			Weeks				Weeks				Weeks				5	6	8
						1	2	3	4	1	2	3	4	1	2	3	4	Σ of 4 periods		
.100	80	5	600	1	1	154	134	81	86	522	402	261	588	88	120	79	51	455	1773	338
	(Q = 24.00 μC)				2	50	23	30	66	282	9	16	131	19	30	31	20	169	438	100
					3	6	38	23	12	157	70	52	96	15	9	13	25	79	375	62
					4	9	14	20	27	129	65	44	91	22	8	6	26	70	329	62
																		773	2915	562
.150	66	5	500	2	1	348	535	563	429	1296	1225	1358	1116	818	813	861	858	1845	4995	3350
	(Q = 24.75 μC)				2	135	389	613	72	1116	1307	1455	184	164	815	752	614	1209	4062	2345
					3	141	31	32	185	1187	205	57	97	42	56	67	401	389	1546	566
					4	111	152	359	231	208	816	533	112	47	367	846	94	853	1619	1354
																		4296	12242	7615
.200	50	5	500	3	1	481	752	714	720	1197	1315	1280	1230	630	861	940	877	2617	5022	3308
	(Q = 25.00 μC)				2	456	790	814	786	1269	1382	1276	1415	228	845	1009	775	2846	5342	2857
					3	258	607	842	692	603	1415	1365	1355	674	803	866	725	2399	4738	3068
					4	461	792	827	702	1137	1337	1407	913	627	962	925	837	2712	4794	3351
																		10694	19896	12584
.250	20	10	500	4	1	237	144	144	139	241	136	85	114	28	52	90	127	664	578	297
	(Q = 25.00 μC)				2	86	348	162	80	150	77	46	77	26	24	27	49	676	350	126
					3	54	145	115	36	85	48	28	52	5	4	30	22	350	213	61
					4	132	329	40	33	80	146	53	83	15	10	9	10	544	362	44
																		2224	1503	528
.100 mA						219	209	154	191	1090	546	373	905	144	167	129	122			
.150 mA						735	1077	1567	917	3807	3553	3373	1509	1071	2051	2526	1967			
.200 mA						1656	2941	3197	2900	4206	5449	5328	4913	2159	3471	3740	3214			
.250 mA						509	906	461	288	558	407	212	326	74	90	156	208			
Per week						3119	5193	5379	4296	9661	9955	9286	7654	3448	5779	6551	5511			
Total responses						17987				36556				21289						

[a] [b] INT. pulse intensity, FREQ. pulse frequency, P.W. pulse width T.D. train duration, Q. - quantity of charge per stimulus
[b] mA milli Ampere
[c] pps pulses per second
[d] ms milliseconds

Fig. 1: Changes in response rate with different pulse intensities, pulse widths, pulse frequencies and train durations; changes expressed as the ratios between the indicated (X) and the lowest parameter values. Broken lines are the means per group.

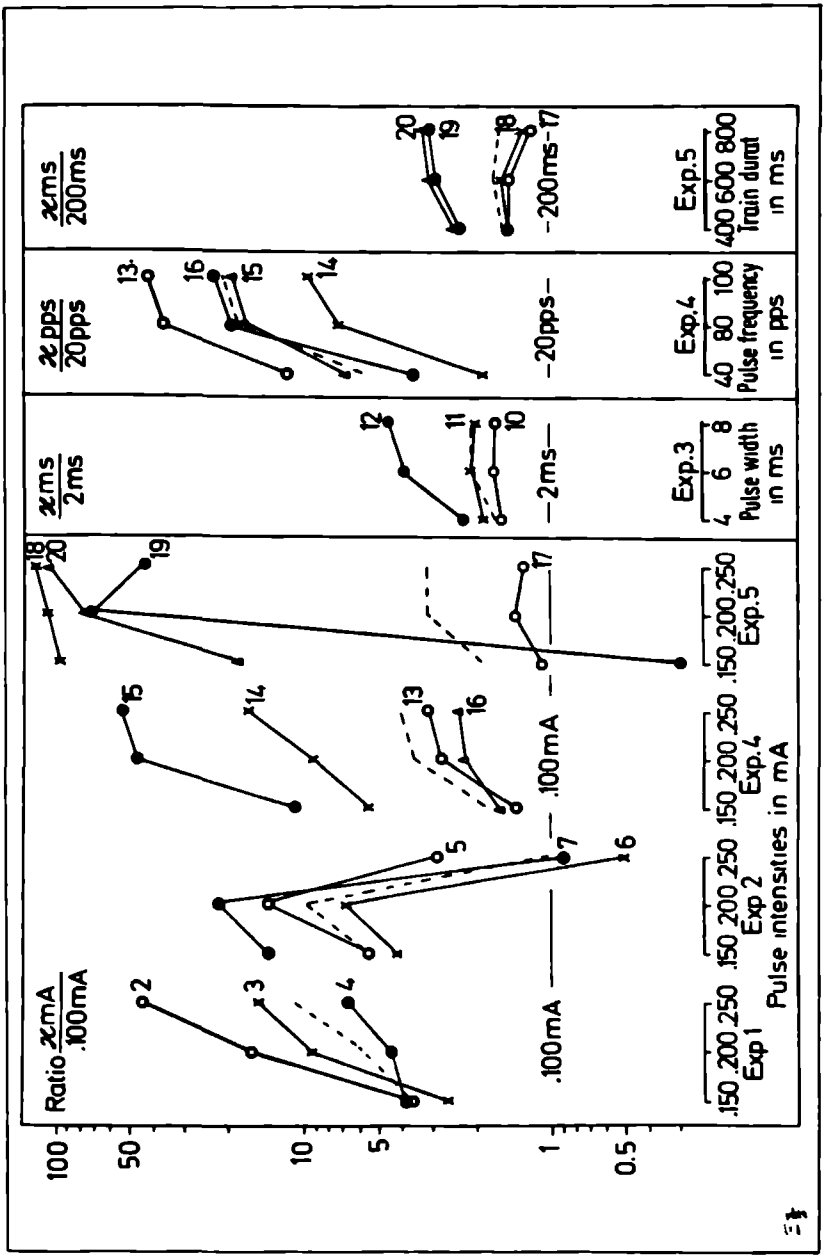


Fig. 2: Changes in response rate during 4 consecutive periods with different intensities (exp. 1: o--o and exp. 2: ●—●) or different pulse widths (exp. 3. x—x). Mean response rates per group of 3 rats expressed as percentages of the responses given during the first period (= 100 %).

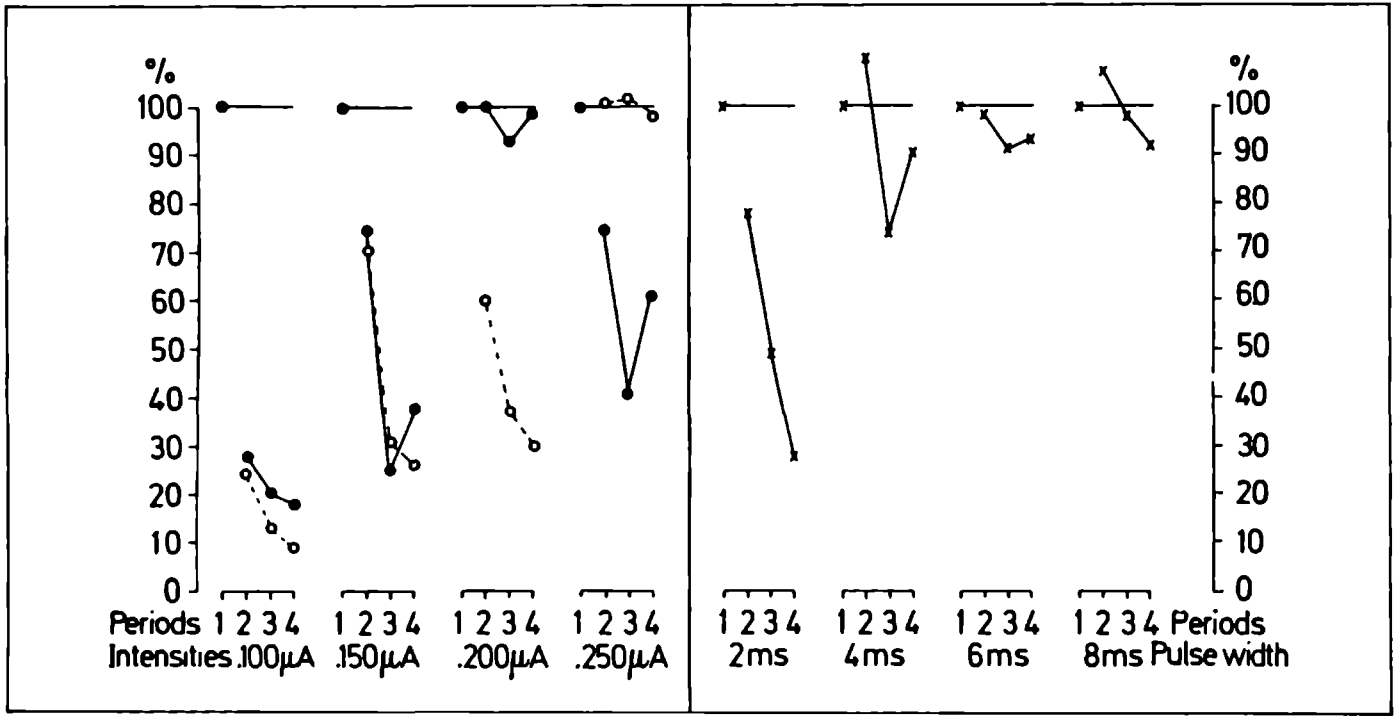


Table 4: *Experiment 3. Variation of pulse width at a constant intensity. Number of responses for 3 trained rats in 16 experimental sessions (4 per week for 4 consecutive weeks). Each session (SES) is divided into 4 periods (PER) of 10 minutes stimulation followed by 1 minute extinction.*

Stimulus parameters[a]				SES	PER	Rat No. 10				Rat No. 11				Rat No. 12				Rat No		
P. W. ms[b]	INT mA[c]	FREQ pps[d]	T. D. ms[d]			Weeks				Weeks				Weeks				10	11	12
						1	2	3	4	1	2	3	4	1	2	3	4	Σ of 4 periods		
2.0	.250 (Q - 12.5 μC)	50	500	1	1	854	997	1184	1114	733	737	854	750	110	255	321	174	4149	3073	860
					2	560	1297	754	1188	478	381	326	923	79	148	94	88	3799	2108	409
					3	224	473	670	1143	273	80	223	545	64	118	52	79	2510	1121	313
					4	22	66	4	1228	89	79	169	289	44	65	54	43	1320	626	206
																		11778	6929	1788
4.0	.250 (Q - 25.0 μC)	50	500	2	1	955	1005	1178	1129	847	848	843	905	509	481	628	209	4267	3443	1827
					2	1262	1301	1190	1212	1099	893	1048	1112	316	186	802	61	4965	4152	1365
					3	1363	1304	26	1253	418	619	632	1045	64	136	108	83	3948	2714	391
					4	1623	1321	1324	1210	435	578	927	816	167	82	135	52	5478	2756	436
																		18658	13065	4019
6.0	.250 (Q - 37.5 μC)	50	500	3	1	1122	1297	1216	1110	824	792	798	870	715	619	660	806	4745	3284	2800
					2	1274	1274	1387	1369	886	907	949	948	300	274	380	660	5304	3690	1614
					3	1157	1161	1264	1390	1085	681	994	888	178	220	476	378	4972	3648	1252
					4	1279	1217	1175	1383	1082	632	1028	843	235	92	548	533	5054	3585	1308
																		20075	14207	7074
8.0	.250 (Q 50.0 μC)	50	500	4	1	1194	1179	1301	1140	731	697	818	788	678	661	782	710	4814	3034	2831
					2	1119	1338	1288	1247	1033	883	966	968	435	824	807	484	4992	3850	2550
					3	1289	1240	1208	1268	811	786	876	1126	481	184	789	368	5005	3599	1822
					4	1255	1121	1260	1304	1010	711	963	988	80	567	416	130	4940	3672	1193
																		19751	14155	8396
2.0 ms						1660	2833	2612	4673	1573	1277	1572	2507	297	586	521	384			
4.0 ms						5203	4931	3720	4804	2799	2938	3450	3878	1056	885	1673	405			
6.0 ms						4832	4949	5042	5252	3877	3012	3769	3549	1428	1205	2064	2377			
8.0 ms						1857	4878	5057	4959	3585	3077	3623	3870	1674	2236	2794	1692			
Per week						16552	17591	16431	19688	11834	10304	12414	13804	4455	4912	7052	4858			
Total responses						70262				48356				21277						

[a] INT. pulse intensity, FREQ. pulse frequency P. W. pulse width T. D. train duration. Q. = quantity of charge per stimulus
[b] ms milliseconds
[c] mA milli Ampere
[d] pps pulses per second

total number of stimuli received was 62370, i.e. a mean of 2.24 responses per stimuli. The individual differences in response rate varied from 21277 to 70262 (Fig. 3).
The response rate was highest in the third week for rat 12 (7052) and in the last week for rat 10 (19688) and 11 (13804). The response rate was lowest in the first week for rat 12 (4455), the second week for rat 11 (10304) and the third week for rat 10 (16431).
The total response rate increased with increasing pulse width from 2 to 8 ms. For rats 10 and 11 responses became more frequent as the pulse width was increased, up to 6 ms. For rat 12 the response rate increased up to a pulse width of 8 ms (Fig. 1).
The response rate decreased during the 4 periods within one session at a pulse width of 2 ms, but remained approximately constant at the pulse widths of 4, 6 and 8 ms, except for rat 12 whose responses decreased even at the highest pulse width of 8 ms (Fig. 2).

Experiment 4. (1) The detailed individual response rates obtained with various pulse frequencies at various intensities and corresponding pulse width, train duration and quantities of charge per stimulation are indicated in Table 5.
The total number of responses given by the 4 rats was 83179, the total number of stimuli being 39539, i.e. a mean of 2.10 responses per stimulus. The individual differences in response rate varied from 7817 to 34510 (Fig. 3).
Response rate increased gradually with increasing intensities regardless of the frequencies, and with increasing frequencies regardless of the intensities (Fig. 1).
The total response rate for the 4 rats gradually increased in direct proportions to the quantity of charge per stimulus from 8 μC onwards, reaching a number of responses up to 50 times the response rate obtained at 4 μC (Table 6). This pattern was mainly determined by rat 16, the response rate of the three other rats being somewhat erratic. A predictably high response rate ( )1000), however, was obtained at and above 16 μC for rat 16, 20 μC for rat 13, 30 μC for rat 15 and 40 μC for rat. 14.

Experiment 5. (2) The detailed individual response rates obtained with various train durations at various intensities and corresponding frequencies, pulse widths and quantities of charge per stimulus are indicated in Table 7.
The total number of responses given by the 4 rats was 135941, the total number of stimuli received 62217, i.e. 2.18 responses per stimulus. The individual differences in response rate varied from 10218 to 67983 (Fig. 3).

(1) Stimulus parameters during training: pulse intensity: .200 to .250 mA; pulse frequency: 50 pps; pulse width: 4 ms; train duration: 500 ms.

(2) Stimulus parameters during training: pulse intensity: .200 to .250 mA; pulse frequency: 80 pps; pulse width: 4 ms; train duration: 500 ms.

Table 5: *Experiment 4. Variation of pulse frequency at various intensities. Number of responses for 4 trained rats in 16 experimental sessions (4 per week for 4 consecutive weeks). Each session (SES) was divided into 4 periods (PER) of 10 minutes stimulation followed by 1 minute extinction.*

Stimulus parameters[a]					Weeks	PER	Rat No. 13				Rat No. 14				Rat No. 15				Rat No. 16				Rat No.			
INT.[b] mA	FREQ pps[c]	P.W ms[d]	T.D ms[d]	Q μC			Sessions				Sessions				Sessions				Sessions				13	14	15	16
							1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	Σ of 4 periods			
.100	20	4	500	4	1	1	36	20	8	2	57	5	17	5	25	18	1	0	24	24	16	13	66	84	44	77
	40	4	500	8		2	26	18	5	13	28	35	10	0	5	17	4	10	27	38	11	14	62	73	36	90
	80	4	500	16		3	213	109	341	107	16	12	18	2	0	0	12	7	727	263	661	194	770	48	19	1845
	100	4	500	20		4	417	609	299	580	17	4	4	10	6	13	3	28	641	837	524	693	1905	35	50	2695
																							2803	240	149	4707
.150	20	4	500	6	2	1	10	11	13	1	25	0	30	6	26	15	12	7	21	6	10	12	35	61	60	49
	40	4	500	12		2	31	28	12	3	37	73	11	2	14	38	0	4	302	194	24	20	74	123	56	540
	80	4	500	24		3	695	305	715	279	308	11	116	0	89	16	132	22	896	812	982	578	1994	435	259	3268
	100	4	500	30		4	247	625	400	557	131	244	147	190	508	322	107	264	858	1041	962	916	1829	712	1201	3777
																							3932	1331	1576	7634
.200	20	4	500	8	3	1	11	35	24	14	4	13	61	42	87	28	38	23	87	16	44	17	84	120	156	164
	40	4	500	16		2	8	301	70	48	2	48	36	47	178	68	18	28	991	733	293	183	427	133	292	2200
	80	4	500	32		3	959	907	968	692	235	196	314	133	918	643	805	982	1153	988	1076	1018	3526	878	3348	4235
	100	4	500	40		4	958	1019	1071	733	231	393	186	324	921	985	784	834	1096	1095	1131	1087	3781	1134	3525	4409
																							7818	2265	7320	11008
.250	20	4	500	10	4	1	33	8	18	9	14	33	26	51	17	21	22	46	255	56	109	34	68	124	106	454
	40	4	500	20		2	770	813	325	533	108	188	49	65	445	289	158	56	951	752	473	297	2441	410	948	2473
	80	4	500	40		3	869	774	737	818	662	318	291	285	803	941	910	880	999	962	1041	1020	3198	1556	3534	4022
	100	4	500	50		4	920	834	790	741	684	622	346	214	833	904	1058	1066	1038	1084	1040	1050	3285	1886	3861	4212
																							8992	3976	8449	11161
			Int. mA	.100			692	756	653	702	118	56	49	17	36	48	20	45	1419	1162	1212	914				
				.150			983	969	1140	840	501	328	304	198	637	391	251	297	2077	2053	1978	1526				
				.200			1936	2262	2133	1487	472	650	597	546	2084	1724	1645	1867	3327	2832	2544	2305				
				.250			2592	2429	1870	2101	1468	1161	712	635	2098	2155	2148	2048	3243	2854	2663	2401				
			Freq. pps	20			90	74	63	26	100	51	134	104	135	82	73	76	387	102	179	76				
				40			835	1160	412	597	175	344	106	114	642	412	180	98	2271	1717	801	514				
				80			2736	2095	2761	1896	1221	537	739	420	1810	1600	1859	1891	3775	3025	3760	2810				
				100			2542	3087	2560	2611	1063	1263	683	758	2268	2224	1952	2192	3633	4057	3657	3746				

[a] [b] INT. pulse intensity FREQ. pulse frequency P.W. pulse width T.D. train duration Q. quantity of charge per stimulus
[b] mA milli Ampere
[c] pps pulses per second
[d] ms milli seconds

Table 6: Experiment 4 Response rate for 4 rats in relation to the quantity of charge per stimulation.

Quantity (µC)[a]	4	6	8	8	10	12	16	16	20	20	24	30	32	40	40	50
Intensity (mA)[b]	100	150	100	200	250	150	100	200	100	250	150	150	200	200	250	250
Frequency (pps)[c]	20	20	40	20	20	40	80	40	100	40	80	100	80	100	80	100
Rat No 13	66	35	62	84	68	74	770	427	1905	2441	1994	1829	3526	3781	3198	3285
14	84	61	73	120	124	123	48	133	35	410	435	712	878	1184	1556	1886
15	44	60	36	156	106	56	19	292	50	948	259	1201	3348	3525	3534	3861
16	77	49	90	164	454	540	1845	2200	2695	2473	3268	3777	4235	4409	4022	4212
Σ of rats	271	205	266	524	752	793	2682	3052	4685	6272	5956	7519	11987	12849	12310	13244
Means			393				2867		5479					12580		
Ratio[d]	1 0	0 8	1 5		2 8	2 9	11		20		22	28	44	46		49

[a] µC micro Coulomb
[b] mA milli Ampere
[c] pps pulses per second
[d] Response at 4 µC = 1 0

Table 7: *Experiment 5. Variation of train duration at various intensities. Number of responses for 4 trained rats in 16 experimental sessions (4 per week for 4 consecutive weeks). Each session (SES) was divided into 4 periods (PER) of 10 minutes stimulation followed by 1 minute extinction.*

Stimulus parameters[a]					Weeks	PER	Rat No 17				Rat No 18				Rat No 19				Rat No 20				Rat No			
							Sessions				Sessions				Sessions				Sessions				17	18	19	20
INT[b] mA	FREQ[c] pps	P W ms[d]	T D ms[d]	Q μC			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	Σ of 4 periods			
100	80	4	200	6 4	1	1	782	24	228	24	6	0	4	1	39	2	4	3	29	4	0	0	1058	11	49	33
	80	4	400	12 8		2	1194	1125	1316	165	7	2	0	4	21	18	3	4	20	24	0	0	3800	13	46	44
	80	4	600	19 2		3	1273	1288	1136	1246	12	8	28	1	5	29	29	7	1	0	15	3	4943	49	43	19
	80	4	800	25 6		4	780	1281	1094	1348	18	1	0	4	11	9	9	13	4	7	5	4	4503	23	46	20
																							14304	96	183	116
150	80	4	200	9 6	2	1	1130	57	477	132	413	201	178	102	10	2	2	4	203	36	42	7	1796	894	18	288
	80	4	400	19 2		2	1240	1191	1408	1465	878	748	170	558	8	1	2	4	659	282	10	10	5304	2354	15	961
	80	4	600	28 8		3	1197	1116	978	1292	900	784	725	898	4	0	2	0	321	52	115	33	4583	3807	6	521
	80	4	800	38 4		4	1025	979	1157	771	681	749	893	710	0	10	6	6	93	208	84	96	3932	3033	22	481
																							15615	10088	61	2251
200	80	4	200	12 8	3	1	1525	1906	2035	49	18	377	598	446	329	59	126	60	410	88	208	26	5515	1439	574	732
	80	4	400	25 6		2	1228	1181	1554	1724	752	689	1046	1034	341	520	187	300	678	467	175	135	5687	3521	1348	1635
	80	4	600	38 4		3	1221	1122	1140	1330	858	920	735	880	443	414	628	529	854	460	1493	660	4813	3395	2014	3467
	80	4	800	51 2		4	1068	835	1142	835	713	676	583	633	404	592	547	839	475	864	1041	978	3880	2605	2382	3358
																							19895	10960	6318	9192
250	80	4	200	16 0	4	1	1525	1662	1624	36	940	895	1035	897	391	26	5	14	675	339	324	160	4847	3767	436	1498
	80	4	400	32 0		2	1527	918	1273	932	869	613	746	965	569	401	22	125	1064	1185	420	832	4650	3193	1117	3501
	80	4	600	48 0		3	1305	1170	958	1302	907	656	438	791	748	204	110	68	1090	310	1055	1572	4735	2792	1130	4027
	80	4	800	64 0		4	1020	740	1066	1111	867	606	437	356	365	228	217	163	1254	1181	950	1110	3937	2266	973	4495
																							18169	12018	3656	13521
			Int mA			100	4029	3718	3774	2783	43	11	32	10	76	35	45	27	54	35	20	7				
						150	4592	3343	4020	3660	2872	2482	1966	2268	22	13	12	14	1276	578	251	146				
						200	5042	5044	5871	3938	2341	2662	2962	2993	1517	1585	1488	1728	2417	2059	2917	1799				
						250	5377	4490	4921	3381	3583	2770	2656	3009	2073	859	354	370	4883	3015	2749	3674				
			T D ms			200	4962	3649	4364	241	1377	1473	1815	1446	769	89	137	81	1317	467	574	193				
						400	5189	4415	5551	4286	2506	2052	1962	2661	939	940	214	433	2421	2138	505	977				
						600	4996	4696	4212	5170	2677	2368	1926	2570	1200	620	769	604	2266	822	2678	2268				
						800	3883	3835	4459	4065	2279	2032	1913	1703	780	843	779	1021	1826	2260	2080	2188				

[a] INT.. pulse intensity, FREQ pulse frequency, P W. pulse width, T D. train duration Q quantity of charge per stimulus
[b] mA milli Ampere
[c] pps pulses per second
[d] ms milliseconds

Table 8: *Experiment 5 Total and individual response rate in relation to the quantity of charge*

Quantity (μC)[a]	6 4	9 6	12 8	12 8	16	19 2	19 2	25 6	25 6	28 8	32 0	38 4	38 4	48	51 2	64 0
Intensity (mA)[b]	100	150	100	200	250	100	150	100	200	150	250	150	200	250	200	250
Train duration (ms)[c]	200	200	400	200	200	600	400	800	400	600	400	800	600	600	800	800
Rat No 17	1058	1796	3800	5515	4847	4943	5304	4503	5687	4583	4650	3932	4813	4735	3880	3937
18	11	894	13	1439	3767	49	2354	23	3521	3307	3193	3033	3392	2792	2605	2266
19	48	18	46	574	436	43	15	46	1348	6	1117	22	2014	1130	2382	973
20	33	288	44	732	1498	19	961	20	1635	521	3501	481	3467	4027	3358	4495
Σ of 4 rats	1150	2996	3903	8260	10548	5054	8634	4592	12191	8417	12461	7468	13686	12684	12225	11671
Means			6081			6844		8391					13175			
Ratio[d]	1 0	2 6	3 4	7 2	9 2	4 4	7 5	4 0	11	7 3	11	6 5	12	11	11	10

[a] μC micro Coulomb
[b] mA milli Ampere
[c] ms milli seconds
[d] Response at 6 4 μC = 1.0

The total response rate for the four rats and for rats 18 and 20 increased with increasing pulse intensity regardless of train duration up to .250 mA for rat 17 up to .200 mA. The response rate was much less regular for rat 19 (Fig. 1).
For the four rats, the lowest response rate occurred with a train duration of 200 ms regardless of pulse intensity and the highest response rate at a train duration of 400 ms for rat 17, at 600 ms for rat 18 and of 800 ms for rat 19 and 20. The total highest response rate was obtained with 600 ms (Fig. 1).
Although higher quantities of charge produced the highest response rates (Table 8), the total response rate was poorly correlated with the quantity of charge, since it was determined by pulse intensity, train duration and the high response rate of rat 17.
A predictably high response rate ( ) 1000) was obtained at and above 6.4 μC for rat 17, 28.8 μC for rat 18 and 48.0 μC for rat 19 and rat 20.

2.3. Discussion

Implantation sites. Fig. 3 shows that the implantation sites for the 17 rats covered a relatively small area in and around the fasciculus medialis prosencephali. Nevertheless the marked individual differences in overall responsiveness and in sensitiveness to selective stimulus parameter combinations indicate the importance of correct implantation, and may reflect the heterogeneity of the stimulated structure (Wetzel, 1970).

Experimental schedule. Although in the fixed ratio reinforcement schedule 2: 1 with T-inhibition, the responses exceeded the stimuli more than twice, the correlation between R and S was ⟩.98 for each individual rat in all 64 sessions.

Pulse intensity. Response rates increased with increasing intensities from .100 to .250 mA (Fig. 1 and Tables 2, 5, 7). At .100 mA the lever pressing frequency was very low in all rats except rat 17, .150 mA elicited a low response rate in about half the rats, whereas the highest response rate was achieved with .200 mA in rats 17 and 19, and with .250 mA in all other rats. However, when the optimal intensities were combined with the low frequency of 20 pps the response rate dropped dramatically (Fig. 1 and 3). Conversely, subthreshold intensities combined with high frequencies enhanced the response rate (Table 5).
Thus the response rate is not exclusively determined by pulse intensity, which indicates that the important factor is not the number but the type of neuronal fibers reached.

Pulse frequency. Response rates increased with increasing frequencies from 20 to 100 pps (Fig. 1 and Table 5). At 20 pps the lever pressing frequency was always very low and could not be improved by high intensities; 40 pps usually produced poor responsiveness which however improved with high intensities; 50 pps usually produced adequate response rates.
Thus individual thresholds of pulse frequency should be reached. More-

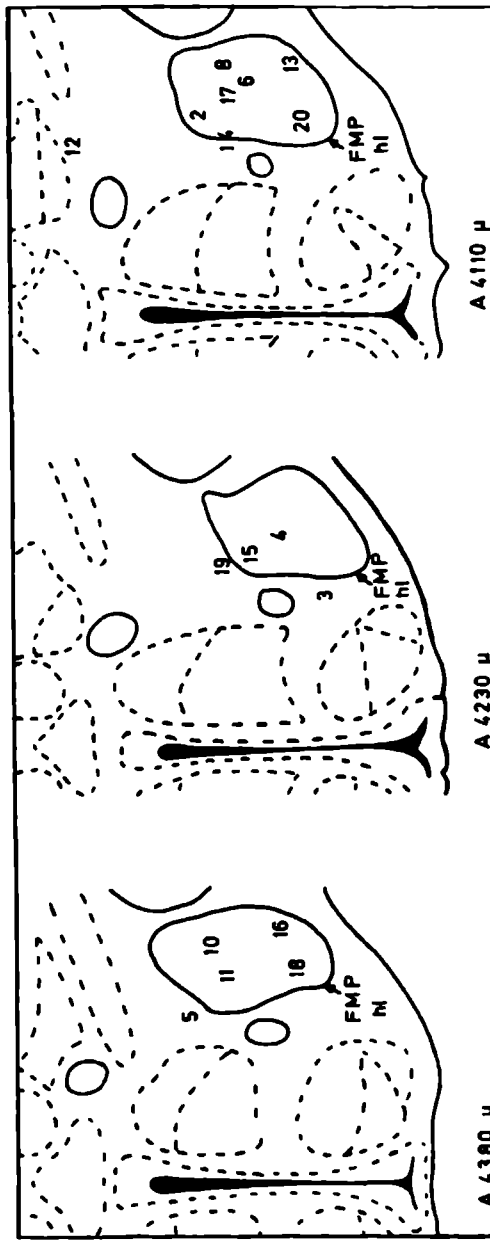
over, since in the stimulus combination of 20 pps x .250 mA frequency outweighs intensity, pulse frequency seems determinative for transmitting the neuroimpulses needed to induce lever pressings, perhaps because a certain amount of neurotransmitter substance has to be deposited in the synaptic cleft.

Pulse width and train duration. At a constant intensity, frequency and train duration, the response rate increased as the pulse width rose from 2 to 6 ms, levelled off at a pulse width of 6 to 8 ms and dropped slightly at a pulse width of 10 ms (Table 4 and compare Table 2 with Table 3).
Optimal response rates occurred with train durations between 400 and 600 ms (Fig. 1 and Table 7); lever pressing frequency was always lower with short train durations (200 ms) and sometimes lower with long train durations (800 ms). In the selected ranges, pulse width and train duration are less critical than pulse frequency and intensity.

Quantity of charge. As reported by Beyra **et al.** (1969a, b), Keesey (1962, 1964), McIntire and Wright (1965), Reynolds (1958), Smith and Cox (1967) and Ward (1959) response rate generally increased with increasing quantities of charge. However, the response rate was not simply a reflection of the quantity of charge (Fig. 4). In experiments 1 and 2 (Tables 2 and 3) although the quantity of charge was kept constant, the response rate varied from low to high. In the five experiments, the quantity of charge varied between 4 μC and 64 μC. Although significant ($p < 0.001$), the correlation between quantity of charge and response rate was rather poor ($r = 0.468$). In addition, low response rates could be obtained with high quantities of charge (24.0 to 49.5 μC) provided the intensities or frequencies were low. Conversely relatively high response rates could be obtained with relatively low quantities of charge (12.5, 12.8 and 16.0 μC), when pulse intensity and frequency were optimal (Tables 4, 6, 7 and 8).

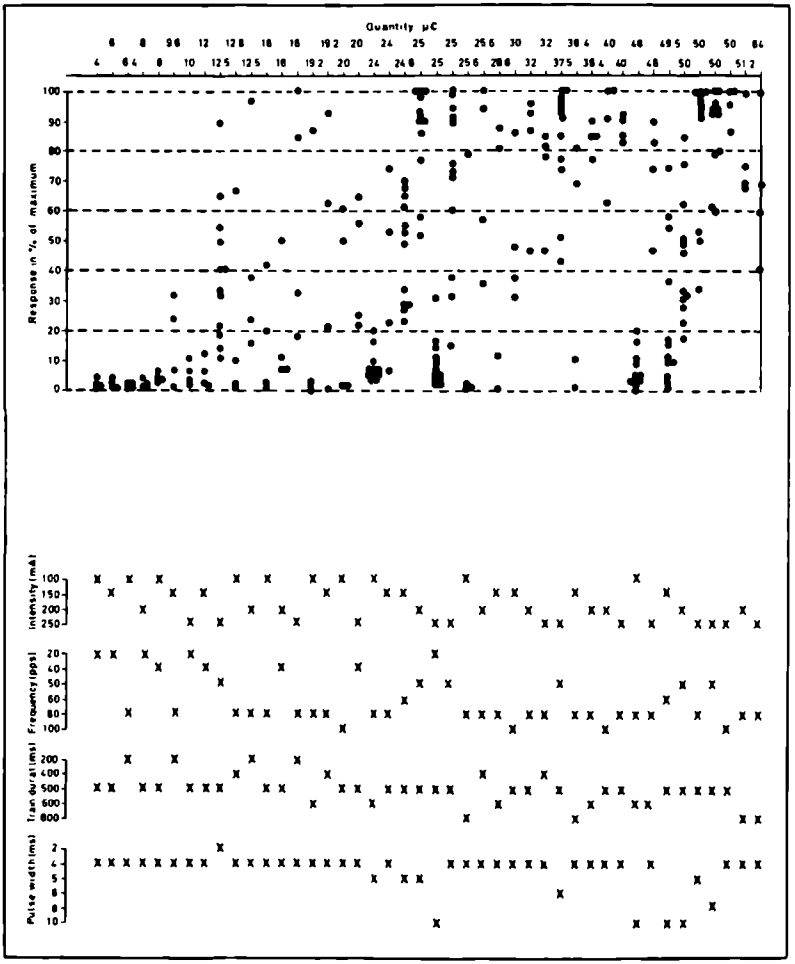
Duration of the experimental sessions and contrast effects
Stimulus parameter combinations were considered optimal if response rates remained at a constant level throughout the four-period sessions (Fig. 2). These stimulus parameter combinations constitute an adequate basis for further investigations.
Although contrast effects, mentioned earlier by Panksepp and Trowill (1969, 1970), occurred when the parameter combination sequence within one session was assigned by a latin square design (Table 1), these contrast effects did not markedly after the response pattern.

Fig. 3: Implantation sites for the 17 rats. Total number of responses, stimuli and ratio responses stimuli. Coordinates according to König and Klippel.
F.M.P. = Fasciculus medialis prosencephali; hl = nucleus lateralis hypothalami.



Rat number	Total number of responses	Total number of stimuli	Response/stimuli	Rat number	Total number of responses	Total number of stimuli	Response/stimuli	Rat number	Total number of responses	Total number of stimuli	Response/stimuli
3	9,006 (11)	4,032	2 23	12	21,227 (11)	10,546	2 02	16	34,510 (44)	16,006	2.16
2	19,318 (22)	9,431	2 05	11	48,356 (21)	21,140	2 29				
4	45,193 (51)	19,780	2 28	10	70,262 (33)	30,684	2 29	19	10,218 (11)	4,773	2 14
5	17,987 (11)	8,618	2 09	14	7,817 (11)	3,851	2 03	20	25,000 (25)	9,745	2.57
8	21,288 (12)	9,510	2 24	15	17,307 (22)	8,210	2 11	18	32,660 (32)	15,792	2 07
6	36,558 (20)	16,550	2 21	13	23,565 (30)	11,472	2 05	17	67,983 (67)	31,907	2 13

Fig. 4: Scattergram of methods and results. Each point represents, for each individual rat, the percent response of the highest response (100 %). The crosses indicate the corresponding parameter combinations in 16 sessions x 17 rats.



VI. The influence of various psychoactive drugs on brain self-stimulation behaviour: an experimental study

1. TEST PROCEDURES

In a quantitative approach to a particular type of behaviour, drug-effects are defined as facilitatory or inhibitory according to whether they increase or decrease base-line behaviour. It may be clear that the assessment of drug-effects is partly dependent upon base-line responding. Because of physical limits to frequency of responding, high levels of base-line responding, for instance, are not suitable for the investigation of facilitatory effects of drugs on responding. As we have demonstrated before, electrical stimulation parameters play an essential role in base-line responding.

Accordingly, different base-lines resulting from different stimulus parameter combinations (SPC's) given during the same session, within the same rats, have been studied.

After self-stimulation had been established during pre-training, rats were selected and further trained on the schedule used for the drug experiments. Criterion for selection was: at least 300 responses per half hour during pre-training.

The schedule used in training and during drug-experiments was as follows: daily one-hour sessions were held, 5 days a week. Each session consisted of six 10-min periods during which rats could obtain brain stimulation by pressing on a lever. The periods were separated by a 1-min «reset-period» during which no brain-stimulation was available. During each period, a different SPC was selected (based on the study of Wauquier et al., 1972, Chapter V.2). Of the six SPC's chosen two elicited low response rates, two high response rates and two intermediate response rates. A fixed ratio-schedule 2:1 was used, i.e. 2 lever-pressings were needed to obtain 1 stimulation (1). Lever-pressings during the stimulation were not rewarded.

Table 1 depicts the different SPC's used. Two stimulators, differring slightly with respect to the SPC's were used (2).

The SPC's were given to groups of 3 rats in a partially randomized sequential order. The sequence of the SPC's is also given in Table 1. The particular sequence given to a rat remained constant during the whole experiment.

(1) This schedule was used in order to minimize the occurrence of seizures occurring when rats get continuous brain-stimulation.

(2) The use of 2 different types of stimulators is purely incidental: the second type of stimulator was developed at a later stage of the research.

Table 1: *Six selected stimulus parameter combinations (SPC) used in pre-drug training and experimental sessions, and the sequence in which they were given.*

SPC stimulator 1		1 L_1	2 L_2	3 M_1	4 M_2	5 H_1	6 H_2
Quantity of charge	(µC)	12.5	16.5	20.0	24.8	31.8	40.0
Intensity	(µA)	250	100	250	150	250	200
Frequency	(pps)	20	66	32	66	50	80
Pulse width	(msec.)	5	5	5	5	5	5
Train duration	(msec.)	500	500	500	500	500	500
Sequence C 1		4	1	5	2	6	3
C 2		6	3	4	1	5	2
C 3		5	2	6	3	4	1
SPC stimulator 2		7 L_1	8 L_2	9 M_1	10 M_2	11 H_1	12 H_2
Quantity of charge	(µC)	10	12	18	20	30	32
Intensity	(µA)	250	100	150	250	250	200
Frequency	(pps)	20	60	60	40	60	80
Pulse width	(msec.)	4	4	4	4	4	4
Train duration	(msec.)	500	500	500	500	500	500
Sequence C 1		4	1	2	5	6	3
C 2		6	3	1	4	5	2
C 3		5	2	3	6	4	1

µC : micro Coulombs
µA : micro Ampères
pps : pulses per second
msec.: milliseconds

L: low
M intermediate
H. high

Training was continued until the rats had adapted to the schedule. Criteria for adaptation were: indications of differential responding on the SPC's and a total of approximately 900 or more responses on the highest SPC's. After training, which required 2 to 3 weeks, drug-experiments were started. Each rat received a solvent on the second day (control-session) and a drug on the fourth day (drug-session); on the first, the third, and the fifth day rats received neither a solvent nor a drug. Starting with the lowest dose in the first week progressively higher doses were given in subsequent weeks.

2. CONTROL RESULTS: ANALYSIS OF VARIANCE

The response rates obtained during the control session are determined by various factors. Because different factors, such as stimulus parameter combinations, subjects, time of experiment and so forth, were manipulated, an adequate analysis of the control data required a factorial approach. An analysis of variance was used to evaluate the data.

2.1. Definition of the variables

Table 2 depicts schematically the different factors involved. A first variable is the **stimulator**, further symbolized as treatment A. This treatment has 2 levels (A_1 and A_2), i.e. two different stimulators have been used.

A second variable is the various **stimulus parameter combinations** (SPC's) (Table 1), and is further symbolized as treatment B. The effects of this treatment are restricted to a single level of A, i.e. B. is nested within A ($B \cap A$). The reason for this is that the two stimulators slightly differed, as regards the possibilities for selecting SPC's. (see Table 1). In Table 2, stimulator 1 corresponds to A_1 and the SPC's 1 to 6 to B_1 ... B_6; stimulator 2 corresponds to A_2 and the corresponding SPC's to B_7 ... B_{12}. For both stimulators, two low SPC's (L_1 and L_2), two intermediate SPC's (M_1 and M_2) and two high SPC's (H_1 and H_2) can be distinguished (see Table 1).

A third variable is the **sequence of the SPC's** further symbolized as treatment C (Table 1) ($C \cap A$).

The fourth variable is the **time** factor, further symbolized as treatment D. D has 5 levels, i.e. the first and the second week (D_1 and D_2) after termination of the training period, one week in the middle of the experimental period (D_3), and the two last weeks of the experimental period (D_4 and D_5). Thus, the selected rats were tested for at least 5 weeks.

The fifth variable is the **subjects**, and is further symbolized by S. The subjects are nested within a treatment combination of A and C ($S \cap AC$). For each AC combination 14 subjects were used, i.e. a total of 84 rats.

2.2. Design

This is a description of the structural model of the design, the expected values of mean squares and the choice of an adequate error term. The treatments A, B, C and D have fixed effects, i.e. all treatment levels about which inferences had to be drawn, were included in the experiment. The subjects (S) were randomly selected from the same population and after implantation randomly assigned to the different treatments (C). It follows that the factorial design used is a mixed model (Model III) (see Kirk, 1968; Huitson, 1966) with both crossed and nested treatments. The following notation rules will be used:

- fixed effects are designated by Greek letters
- random effects are designated by Roman letters

Table 2: *Schematic representation of the different treatments and the repartition of the subjects within the treatment combinations.*

	A_1			A_2		
	C_1	C_2	C_3	C_4	C_5	C_6
	$b_1 \ldots b_j \ldots b_6$	$b_1 \ldots b_j \ldots b_6$	$b_1 \ldots b_j \ldots b_6$	$b_7 \ldots b_j \ldots b_{12}$	$b_7 \ldots b_j \ldots b_{12}$	$b_7 \ldots b_j \ldots b_{12}$
	$s_1(11) \cdots S_m(11) \cdots S_{14}(11)$	$s_1(12) \cdots s_m(12) \cdots S_{14}(12)$	$s_1(13) \cdots s_m(13) \cdots s_{14}(13)$	$s_1(24) \cdots S_m(24) \cdots s_{14}(24)$	$S_1(25) \cdots S_m(25) \cdots s_{14}(25)$	$S_1(26) \cdots S_m(26) \cdots S_{14}(26)$
d_1						
d_2						
d_3						
d_4						
d_5						

- nested effects are indicated by adding the subscripts between brackets the symbols referring to the particular level of the treatment(s) within which they are nested.

The effects of the levels of the different treatments are designated as follows:

A:	α_1	α_i	α_p	(p = 2)	(fixed crossed effects)
B.	$\beta_{1(i)}$	$\beta_{j(i)}$	$\beta_{q(i)}$	(q = 6)	(fixed nested effects)
C:	$\gamma_{1(i)}$	$\gamma_{k(i)}$	$\gamma_{r(i)}$	(r = 3)	(fixed nested effects)
D:	δ_1	δ_u	δ_t	(t = 5)	(fixed crossed effects)
S:	$s_{1(ik)}$	$s_{m(ik)}$	$s_{s(ik)}$	(s = 14)	(random nested effects)

Let X_{ijkuma} be a measure for a randomly selected observation «a», in a treatment population $ABCDS_{ijkum}$. Under the mixed-effects model, it is assumed that measurement X_{ijkuma} is equal to the following terms:

$X_{ijkuma} =$

$$\mu + \alpha_i + \beta_j + \gamma_{k(i)} + \delta_u + s_{m(ik)} + \alpha\delta_{iu} + \beta\gamma_{jk(i)} + \beta\delta_{ju(i)} + \beta s_{jm(ik)} + \gamma\delta_{ku(i)} + \delta s_{um(ik)} + \beta\gamma\delta_{jku(i)} + \beta\delta s_{jum(ik)} + \epsilon_{a(ijkum)}$$

where μ: grand mean for treatment populations

α_i, β_j, $\gamma_{k(i)}$, and $sm(ik)$:

- effects of the different treatments;

$\alpha\delta_{iu}$, $\beta\gamma_{jk(i)}$, $\beta\delta_{ju(i)}$, $\beta s_{jm(ik)}$, $\gamma\delta_{ku(i)}$, $\delta s_{um(ik)}$ and

$\beta\gamma\delta_{jku(i)}$, $\beta\delta s_{jum(ik)}$

- effects that represent non-additivity of the stated effects (respectively first and second order interactions);

$\epsilon_{a(ijkum)}$

- experimental error, which is **normally** and **independently** distributed with mean = 0 and variance = σ^2_ϵ (within cell error term).

The expected values of the mean squares $[E\ (MS)]$, are determined according to the general rules described by Kirk (1968) and given in Table 3.

However, in this design only one observation is available for each treatment combination (1 ... a ... n: N = 1). For such an experiment a mean square within cell ($\epsilon_{a\ (ijkum)}$) term cannot be computed. Therefore, the pooled highest-order interaction(s), instead of the within-cell error term, is used as an estimate of the experimental error.

Table 3: The expected values of mean squares [E(MS)], determined according to the general rules described by Kirk (1968).

Effects	E(MS)	Degrees of freedom	Error term n > 1	Error term n = 1
(1) α_i	$\sigma_\epsilon^2 + qtn\,\sigma^2_\alpha + qrstn\,\sigma_\alpha^2$	p-1	5	5
(2) β_j	$\sigma_\epsilon^2 + tn\,\sigma^2\beta s + rstn\sigma_\beta^2$	p(q-1)	9	9
(3) $\gamma_{k(i)}$	$\sigma_\epsilon^2 + qtn\sigma^2 s + qstn\sigma^2\gamma$	p(r-1)	5	5
(4) δ_u	$\sigma_\epsilon^2 + qn\sigma^2\delta s + pqrsn\sigma^2\delta$	t-1	11	11
(5) $s_{m(ik)}$	$\sigma_\epsilon^2 + qtn\sigma^2 s$	pr(s-1)	14	(12 + 13)
(6) $\alpha\delta_{iu}$	$\sigma_\epsilon^2 + qn\sigma^2\delta s + qrsn\sigma^2\alpha\delta$	(p-1)(t-1)	11	11
(7) $\beta\gamma_{jk(i)}$	$\sigma_\epsilon^2 + \gamma n\sigma^2\beta s + stn\sigma^2\beta\gamma$	p(q-1)(r-1)	9	9
(8) $\beta\delta_{ju(i)}$	$\sigma_\epsilon^2 + n\sigma^2\beta\delta s + rsn\sigma^2\beta\delta$	p(q-1)(t-1)	13	(12 + 13)
(9) $\beta s_{jm(ik)}$	$\sigma_\epsilon^2 + \gamma n\sigma^2\beta s$	pr(q-1)(s-1)	14	(12 + 13)
(10) $\gamma\delta_{ku(i)}$	$\sigma_\epsilon^2 + qn\sigma^2\delta s + qsn\sigma^2\gamma\delta$	p(r-1)(t-1)	11	11
(11) $\delta s_{um(ik)}$	$\sigma_\epsilon^2 + qn\sigma^2\delta s$	pr(t-1)(s-1)	14	(12 + 13)
(12) $\beta\gamma\delta_{jku(i)}$	$\sigma_\epsilon^2 + n\sigma^2\beta\delta s + sn\sigma^2\beta\gamma\delta$	p(q-1)(r-1)(t-1)	13	}
(13) $\beta\delta s_{jum(ik)}$	$\sigma_\epsilon^2 + n\sigma^2\beta\delta s$	pr(q-1)(t-1)(s-1)	14	}
(14) $\epsilon_{a(ijkum)}$	σ_ϵ^2	pqrts(n-1)		

2.3. Some remarks concerning the fundamental assumptions in the analysis of variance

Cochran and Cox (1957) stated that failure to meet the fundamental assumptions affects both the significance level (in both directions) and the sensitivity of the test. However, the F-distribution is very robust with respect to violation of these assumptions. Cochran (1947) stated that it is impossible to be certain that all required assumptions are satisfied. Analysis of variance must therefore be regarded as approximate rather than exact (Kirk, 1968). One of the requirements for a ratio of variances in order to obey the F-distribution is that the numerator and denominator of the ratio are independent. If scores are randomly sampled from a normal population, this requirement is satisfied. The errors also have to be normally distributed for each treatment population. Because the only source of variation within a treatment population are the errors, the above mentioned assumption is equivalent to the assumption of normally distributed scores. Fortunately, the F-distribution is relatively unaffected by lack of symmetry or by kurtosis, provided the populations are homogeneous in form (Lindquist, 1953).

The F-distribution is robust with respect to violation of the assumptions of homogenity of population-error variances, provided the number of observations in the samples is equal (Cochran, 1947; Lindquist, 1953).
A further basis assumption of the particular statistical model used to analyze the present data, is that a score is the **sum** of the effects of the linear model. A particular situation occurs when the number of within-cell observations is 1, as is the case in the present model. As pointed out, the higher order interactions are considered to be zero. Thus the corresponding E (MS) of these terms yields an estimate of experimental error. This means that $\sigma^2\beta\gamma s$ and $\sigma^2\beta\gamma\delta$ are supposed to be 0. If this is true, the E (MS) for effects (12) and (13) (see Table 3) are both estimates of σ^2_ϵ The mean square for the experimental error term is calculated by pooling the SS of (12) and (13), i.e. MS (12 + 13) =

$$\frac{SS_{12} + SS_{13}}{\delta f_{12} + \delta f_{13}} = \text{MS residual.}$$

The basic question to be answered is: are the higher-order interactions equal to zero? Some **a posteriori** remarks concerning this assumption will be discussed in the next section.

2.4. Results

The results of the analysis of variance are shown in Table 4. The following factors were significant: stimulus parameter combinations (B) ($p < .01$), time (D) ($p < .01$) and subjects (S) ($p < .01$). The following interactions were significant: stimulus parameter combinations x sequence (B x C) ($p < .05$), stimulus parameter combinations x subjects (B x S) ($p < .01$), and time x subjects (D x S) ($p < .01$).
In the present table of variance, the MS residual was found by pooling the variance of the second order interactions B x C x D (within A) and B x D x S (within AC) (respectively effects 12 and 13 in Table 3). If the MS's are calculated for these interactions, then we find:

27 382.6488 for BCD (within A) (effect 12) and,
29 413.4742 for BDS (within AC) (effect 13).

The E (MS) for these effects are respectively:
(12) $\sigma^2_\epsilon + n\sigma^2\beta\delta s + sn\sigma^2\beta\gamma\delta$
(13) $\sigma^2_\epsilon + n\sigma^2\beta\delta s$
If the interaction term $\sigma^2\beta\delta s$ is equal to zero, the F-ratio of effect 12 to effect 13, should be significant. By contrast, the F-ratio is even slightly smaller than 1, proving that the assumption should not be rejected.
From the present design, no such exact test can be derived for the assumption that $\sigma^2\beta\delta s$ is equal to zero.
If $\sigma^2\beta\delta s$ is not equal to zero, the error variance will be overestimated and an F-test involving $\sigma^2\beta\delta s$ in the denominator will be negatively biased. On the contrary, if a significant F-ratio is obtained, one can be confident that there are real treatment differences. This is exactly the case in the

Table 4: Analysis of variance table.

Source of variation	Sum of squares	df	Mean squares	F	
(1) A	632 922.210	1	632 922.210	(1/5)	0.723
(2) B (within A)	310 011 501.391	10	31 001 150.139	(2/9)	130.415**
(3) C (within A)	8 191 105.027	4	2 047 776.257	(3/5)	2.340
(4) D	2 038 725.140	4	509 681.285	(4/11)	5.335**
(5) S (within AC)	68 246 111.355	78	874 950.146	(5/12)	29.847**
(6) A x D	254 704.844	4	63 676.211	(6/11)	0.667
(7) B x C (within A)	8 538 556.925	20	426 927.846	(7/9)	1.796*
(8) B x D (within A)	1 444 287.263	40	36 107.182	(8/12)	1.232
(9) B x S (within AC)	92 707 544.317	390	237 711.652	(9/12)	8.109**
(10) C x D (within A)	1 051 850.902	16	65 740.681	(10/11)	0.688
(11) D x S (within AC)	29 808 017.846	312	95 538.519	(11/12)	3.259**
(12) Residual	48 075 631.605	1640	29 314.410		
Total	571 000 958.825	2519	-		

* $p \leq 0.05$
** $p \leq 0.01$

present analysis of variance. All effects tested against MS residual are significant at $p < .01$. There is only one exception, i.e. the B x D (within A) interaction. However, in this test, no negative bias can occur, as $\sigma^2_{\beta\delta s}$ appears both in the numerator and in the denominator of the F-ratio /see Table 3: E (MS)/.

2.5. Discussion

The factor B, effects of the SPC's, was found significant ($p < .01$). Fig. 1 shows the mean response rates per SPC for stimulator 1 and 2.
In general, the higher the quantity of charge of the SPC, the higher the response rates (see also Wauquier et al., 1972, Chapter V). The response rates obtained on stimulator 1 are slightly higher than those obtained on stimulator 2. Although not significant (see factor A), this difference could depend on the higher quantity of charge of the SPC's of the first stimulator (see Table 1). There is a tendency to obtain higher total response rates with sequences starting with a low SPC (C_1 and C_4) and the lowest total response rate with those starting with high SPC's (C_3 and C_6) (see Fig. 2). However, the difference is not significant. The interaction B x C was significant ($p < .05$) and is illustrated in Fig. 3. This clearly shows that the effects of factor B (SPC's) will differ according to the sequence in which they are tested. The most marked differences occurring for both stimulators, are the higher response rates for B_2 and B_8 with sequence C_1 and C_4 respectively, and for B_5 and B_{11} with sequence C_3 and C_6 respectively.

Fig. 1: Mean response rates per SPC (L: low, M: intermediate; H: high; see details Table 1) for stimulator 1 and 2.

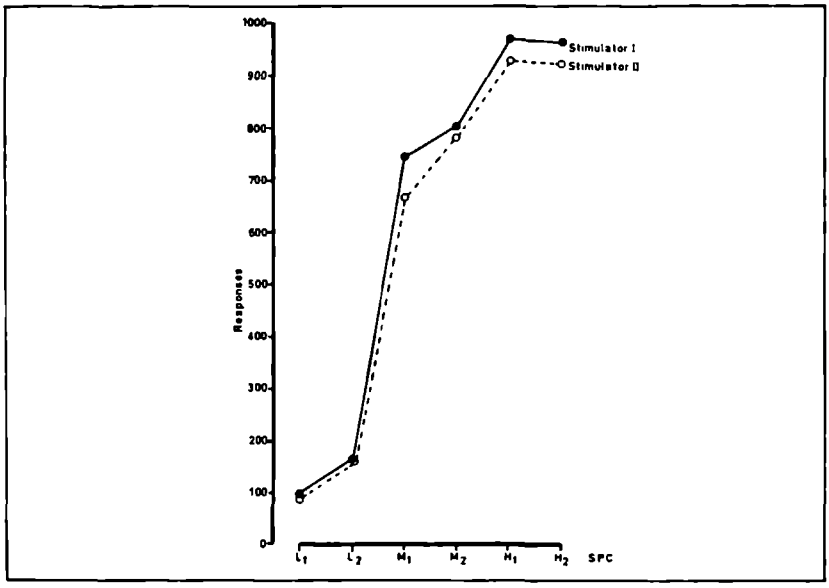


Fig. 2: Total response rates (sum 6 SPC's) in function of the sequence of the SPC's: sequence 1: low SPC (C_1, C_4); sequence 2: intermediate SPC (C_2, C_5); sequence 3: high SPC (C_3, C_6), given at the start of the session.

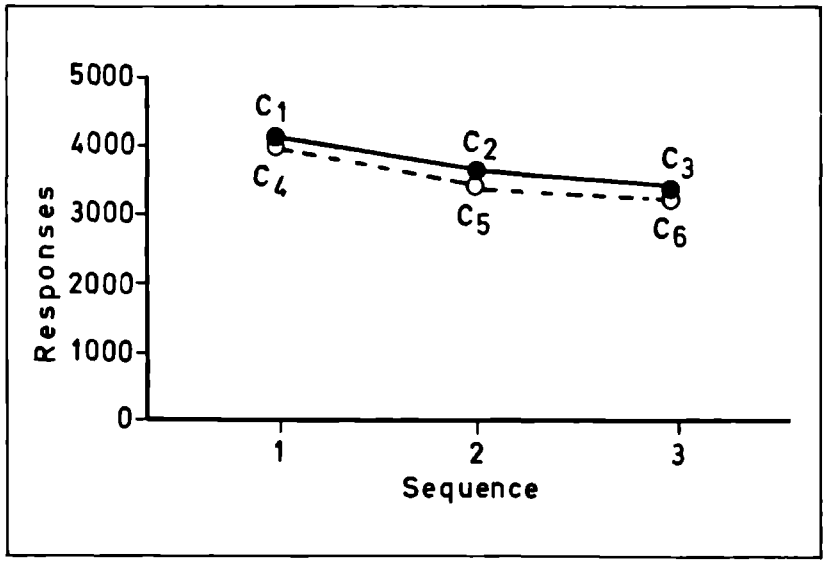
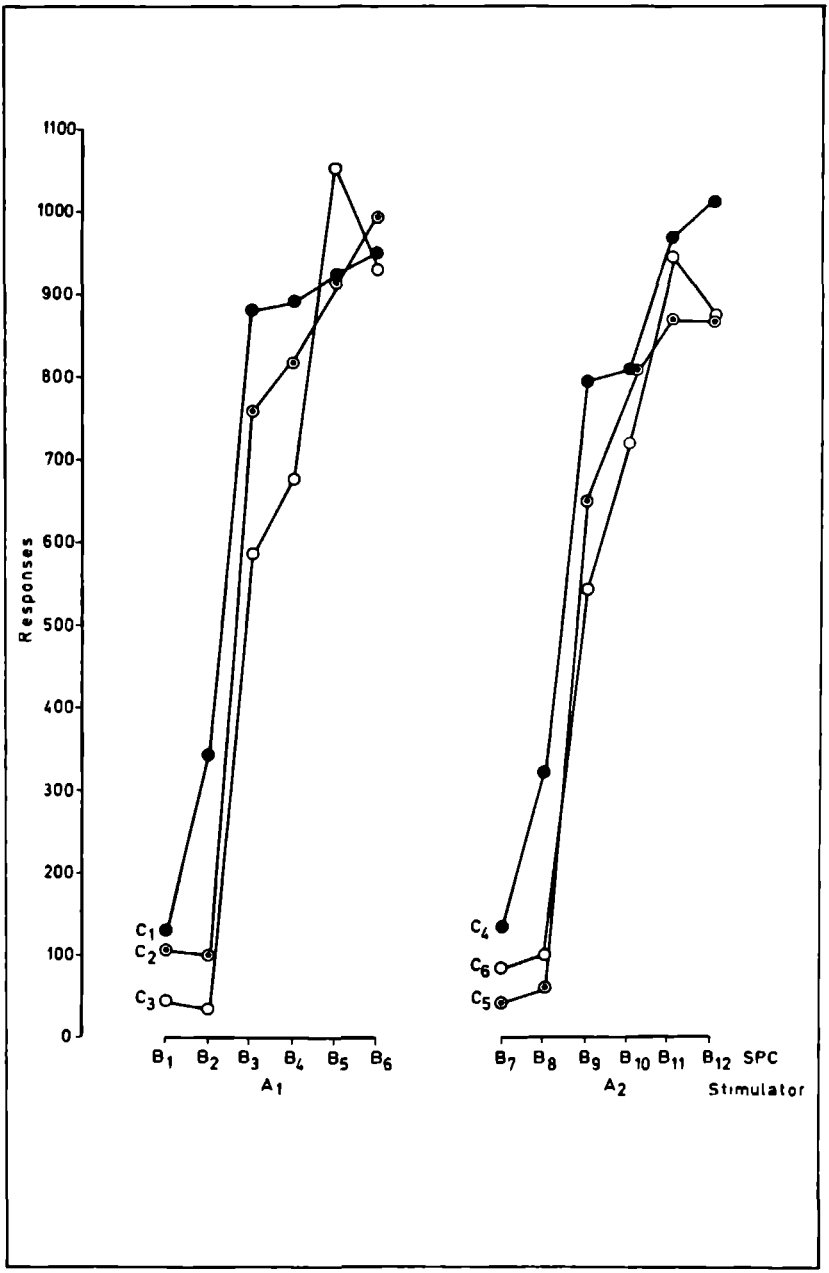


Fig. 3: Interaction B (SPC) x C (sequence).
Mean response rate in function of stimulator (A_1, A_2), SPC's (B_1 ... B_6 and B_7 ... B_{12}) and sequence (C_1 ... C_6).



Higher or lower responding caused by reward shifts are described in the literature (Panksepp and Trowill, 1969). The reinforcing value of the different SPC's may be dependent on the sequence in which they are tested and actually produce higher or lower responding. However, the present shifts cannot clearly be interpreted because all possible sequences of the SPC's were not tested.

The factor time (D) was significant ($p < .01$). As seen in Fig. 4 the further response rates increased slightly from the first to the second week of testing, and subsequently decreased over the following weeks. It is of interest to note that the analysis was done on rats which had been tested for 5 weeks, as well as on rats which had been tested for longer periods. The latter increases the possibility of response decline, so that the actual results may underestimate the response decrease as a function of time. For the progressive decrease in responding as a function of time two explanations are possible. The first explanation refers to the fact, that the rats received drug-treatment between control sessions. Drug-treatment can cause shifts in control values, which outlast direct drug-effects. For example, chlordiazepoxide markedly enhanced responding during the days following drug-injection (Wauquier, 1974). A second explanation for the decline in responding as a function of time may be found in the possibility, that prolonged electrical stimulation induces lesions in the brain structures stimulated.

The factor subjects (S) was found significant ($p < .01$). The total response rates emitted by the subjects, varied over a large scale. The variability in sensitivity to brain-stimulation was described previously (see, for example, Wauquier et al., 1972, Chapter V.2) and various reasons for this were described above see Chapter IV-4).

The significant interaction B x S (SPC's x subjects) ($p < .01$) pointed to the fact that, for individual rats, there are qualitatively different relationships between the quantities of charge (SPC's) and response rates. For instance, some rats exhibit no further increase, or even a decrease of responding at the highest SPC's because the limits of performance are reached, or because the stimulation becomes aversive.

Further, large differences with respect to the evolution of responsiveness as a function of time, are observed for individual rats. Consequently, the interaction D x S (time x subjects) was found significant ($p < .01$).

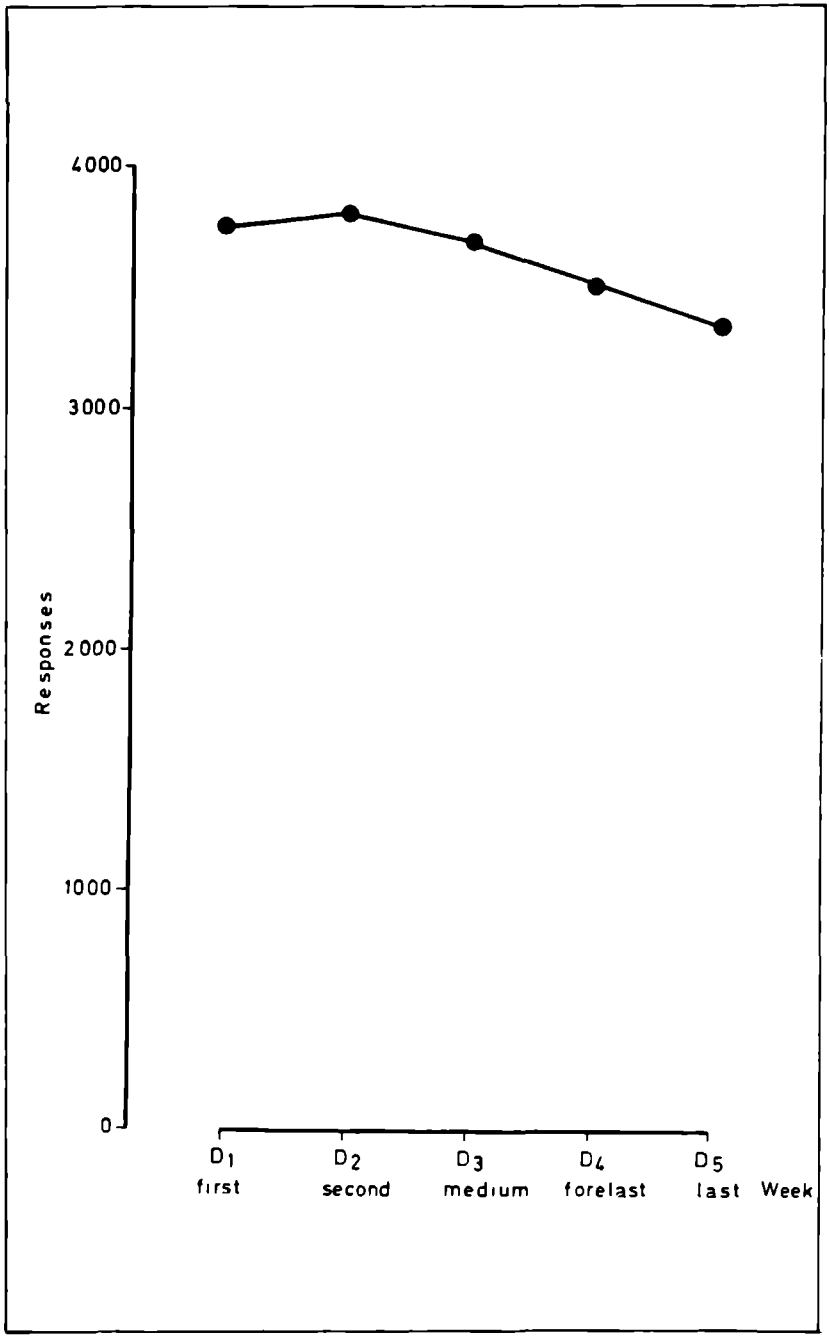
In conclusion: Because of the significant effects of the factors B (SPC's), D (time) and S (subjects) and the significant interactions in which these factors are involved, **it is absolutely necessary to relate data possibly involving drug effects to control data obtained (a) in the same rats, (b) for the same SPC's and (c) during the same week.**

3. DRUG EFFECTS*

3.1. Introduction

In total, 38 compounds were investigated; each compound was given in 3 to 6 doses and each dose was tested on 3 to 6 rats. The effects

Fig. 4: Total response rates as a function of time (D_1 ... D_5).



obtained with the 20 neuroleptics are extensively described in Chapter VII.

As was mentioned before, each rat in our investigation received a drug on the fourth day of each week. For each rat, for each dose of the various drugs used and for each SPC, the response rates obtained during the drug session (the fourth day of the week) were expressed as percentages of the response rates obtained during the control session (the second day) of the same week. As a test for significance of differences between drug- and control-response rates obtained with the different rats on each SPC-dosis combination, the Wilcoxon matched-pairs signed-ranks test, one-tailed probability (Siegel, into consideration 1956, pp. 75-83) was applied. It is of interest to note that the test takes the direction as well as the magnitude of the differences between control- and drug-treatment.

The material in the following sections is organized as follows: each section, which pertains to a class of drugs, is introduced briefly; the results of the drug-experiment are represented in a figure and followed by a description of the results; finally, the results are discussed with respect to the findings reported in the literature.

The figures are constructed as follows:

the generic name of the drug, the chemical formula, the injection route, the injection time (in min before the session) and the number of rats (n) are indicated at the top of the figure; the response rates obtained with all rats on each SPC and after each dose of a drug during the drug session (fourth day of the week) are expressed in percentages of the control response rates obtained during the control session (second day of the week). Significant ($p < .05$) differences are indicated by an asterisk. Note that the statistical test could not be applied where only 3 rats were used.

The reasons for analysing the data separately for each dose and for each SPC are the following: a) some doses of a particular drug may cause response enhancement (RE), other doses of the same drug may cause response decrease (RD); b) RE and RD are base-line dependent; as we have seen before, different SPC's induce different levels of base-line responding. So, on each of the parameters described, RE as well as RD may be found. Finally, significant RE and RD may be partly determined by the sensitivity of the individual rats to drug effects.

3.2. CNS-stimulants (1)

Amphetamine, cocaine and apomorphine are central stimulants inducing stereotype behavior and agitation in various animal species. Animals tend to self-administer these drugs if they are offered the opportunity to do so; cocaine and amphetamine possess abuse liability in humans.

* This chapter is based on Wauquier (1976a).

(1) The results of this investigation have already been published (Wauquier and Niemegeers, 1973, 1974a,b).

3.2.1. Cocaine (Fig. 5)

Cocaine induces a dose-related facilitation of self-stimulation. Thus, the higher the dose, the higher the RE. The RE is predominantly observed on the SPC's inducing low control response rates and approximately the same on SPC 1 and 2. Cocaine does not cause any significant RD.

There are individual differences between the rats with respect to the sensitivity to cocaine-induced RE. Some low responders are more sensitive to RE. However, there is no direct relationship between RE and/or RD and the individual control response rates.

In contrast to the effects of amphetamine and apomorphine (see 3.2.2., 3.2.3.), no difference is found between the effects of cocaine on the first and second half hour of the session.

3.2.2. Amphetamine (Fig. 5)

All doses of amphetamine preferentially induce RE. The highest RE is observed with 0.63 mg/kg, higher doses causing a somewhat lower RE. Low control response rates are more susceptible to RE. On increasing the dose of amphetamine one also observes a gradually increasing RD. This effect is most pronounced on the SPC's inducing high response rates. There is no direct relationship between the response rates obtained in each individual rat and RE or RD.

With the doses 0.16 and 0.31 mg/kg of amphetamine no apparent behavioural changes are seen; 0.63 mg/kg produces a slight increase in sniffing, rearing and ambulation. Increasing the dose of amphetamine results in a gradually and more pronounced stereotype locomotor activation, but chewing movements are not observed. The peak intensity is reached between 50 and 90 minutes after injection.

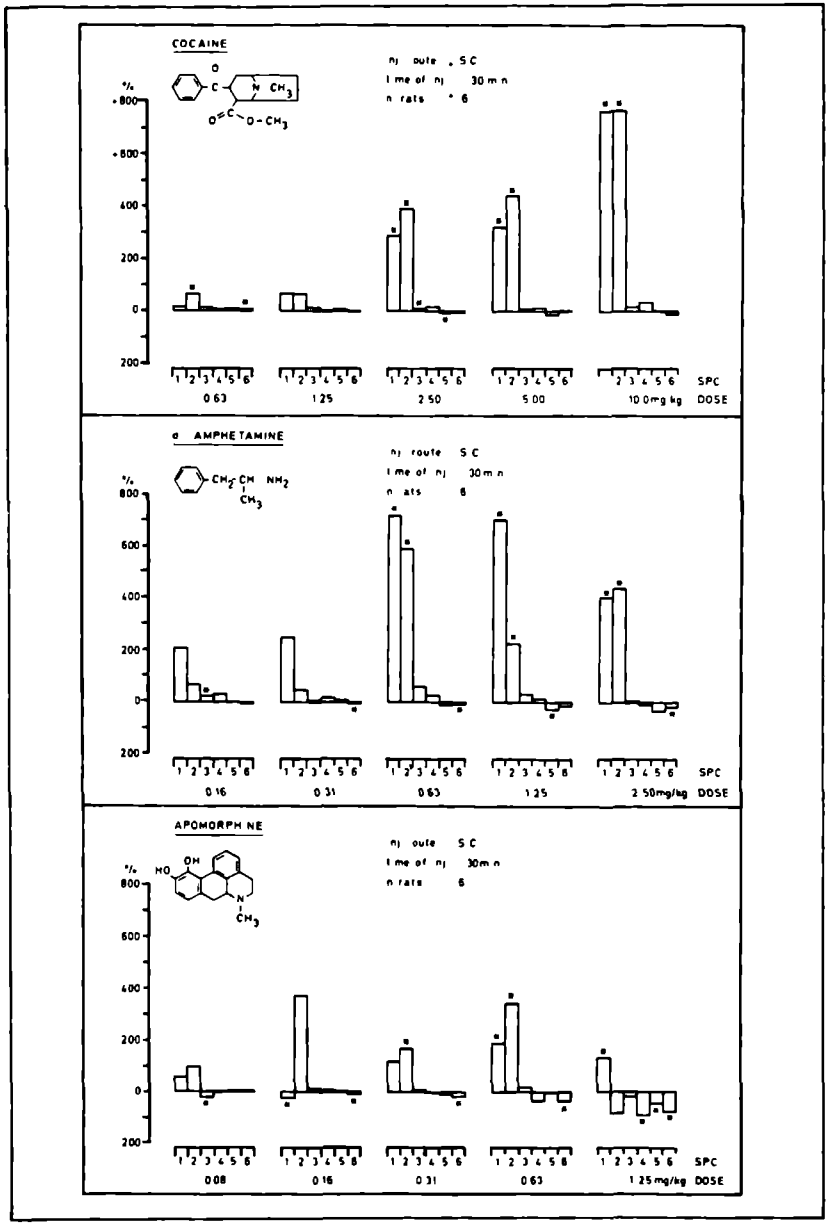
Concomitant with these observations, RE is most pronounced during the second half hour of the session, while RD found with 1.25 and 2.50 mg/kg of amphetamine also increased during the second half hour of the session. With the two highest doses, rats pressed the lever at nearly equal rates regardless of the particular SPC given.

3.2.3. Apomorphine (Fig. 5)

With apomorphine RE and RD are dose-related. The highest RE is obtained with 0.63 mg/kg and the highest RD with 1.25 mg/kg. RE is most pronounced at the SPC's inducing low control response rates, while RD is most pronounced at the SPC's inducing high control response rates. Whereas RD is not related to the individual control response rates, RE is directly related. The higher the control response rates, the higher the RE. Apparently, rats sensitive to brain-stimulation (low threshold, high responders) are more susceptible to the facilitating effects of apomorphine. This was confirmed in additional experiments using high and low responders at low frequency stimulation.

RD is most pronounced during the first half hour of the session, and RE during the second half hour of the session. The time-course of these effects corresponds with the stereotype behaviour induced with 0.31, 0.63 and 1.25 mg/kg of apomorphine, lasting for 40, 50 and 60 min respectively.

Fig. 5: Response rates (all rats combined) in percentages of the respective control response rates, obtained with different doses (mg/kg) and for each stimulus parameter combination (SPC) with cocaine, dl-amphetamine and apomorphine. Chemical structure, injection route, time of injection and number of rats tested are indicated at the top of the figure



3.2.4. Discussion

The effects of the CNS-stimulants cocaine, amphetamine and apomorphine are dependent on the dose, the time of measurement after injection and the base-line rate. These drugs facilitate and/or depress leverpressing for brain-stimulation. There are, however, marked differences between the 3 compounds. Facilitation is most pronounced with cocaine and lowest with apomorphine. Depression is not found with cocaine, but with amphetamine and most pronounced with apomorphine. As far as neurotransmission is concerned, it can be stated that cocaine, amphetamine and apomorphine all have a common denominator: they influence dopaminergic systems. This does not exclude the involvement of other neurotransmitters such as NA and SHT. Cocaine was reported to block the uptake of DA (Hamberger and Masuoko, 1965; Ross and Renyi, 1967), amphetamine, to release DA (Stein, 1964a) and apomorphine to stimulate DA receptors directly (Ernst, 1965). The compounds having synergistic action with cocaine or amphetamine could either enhance the available DA (MAO-inhibitors, tricyclic antidepressants and some antihistamines) (Benešová, 1969), or antagonize the inhibitory cholinergic system (anticholinergics) interacting with the nigrostriatal dopaminergic system. NA-antagonists (phenoxybenzamine and propranolol) only moderately antagonize the amphetamine-induced facilitation (Pradhan, 1976), whereas DA-receptor blockers (specific neuroleptics) are potent inhibitors of amphetamine- or apomorphine-induced stereotype behaviour (e.g. Janssen et al., 1967; see also further 4 and Chapter VII).

3.2.5. Discussion

The doses of amphetamine and apomorphine which cause depression of high rates of self-stimulation induce stereotype behaviour. The time course of the depression coincides with the time course of stereotypy. At high doses of apomorphine, self-stimulation is severely interrupted. At high doses of amphetamine, self-stimulation is not completely inhibited. The rats press the lever at lower rates for high SPC's and at higher rates for low SPC's; the self-stimulation rate is rather independent of the particular SPC used. In addition, amphetamine-treated rats show a strong resistance to extinction (Olds, 1970). Broekkamp (1976) also observed that apomorphine-treated rats continue to press the lever, even when brain-stimulation is no longer supplied.

Apparently, the rats lost their adaptation to the situation, and this loss resulted in facilitation, depression and perseverant lever-pressing. This may, to some extent, be due to a competition between lever-pressing and stereotype behaviour. Further, direct receptor activation (apomorphine) is more disrupting for adapted behaviour than the non-stimulation contingent release of catecholamines (amphetamine).

Stereotype behaviour is characterized by the reduction of a behavioural pattern to fragmentary behaviour during which restricted particular movements predominate. By means of the continuous drug-action other behavioural elements not related to lever-pressing behaviour may be reinforced. The CNS-stimulants, in addition, may change response-related cues, which tend to enhance the disruption of lever-pressing.

The perseverant responding when the stimulation is switched off, can hardly be explained in terms of a competition between lever-pressing and stereotype behaviour. Lever-pressing, when there is no reinforcing brain-stimulation is, in a certain sense, itself, a stereotype act, the only source of reinforcement being the drug. The CNS-stimulants used here have apparently reinforcing properties of their own. This is demonstrated by the fact that rats and other species self-administer these drugs. Further, except for apomorphine, these drugs possess abuse liability.
An alternative, and maybe more likely interpretation for the perseverant responding when the stimulation is switched off, is that rats fail to habituate. The performance of such rats is like the performance of rats extensively lesioned in forebrain structures (Huston and Ornstein, 1976). It appears that CNS-stimulants cause a «functional lesion».
The facilitation of responding is independent of the type of the response. The stimulants increase the frequency of many differently reinforced responses (see e.g. the noise-escape situation in which lever-pressing and jumping were alternated during the same session, Niemegeers et al., 1972). Liebman and Butcher (1973) described how apomorphine caused depression of self-stimulation, which was restored to control levels on doubling the current. According to these authors, their data suggest a deficit in reward. However, the facilitation of lever-pressing is not specifically related to the positive motivation involved in brain self-stimulation. The CNS-stimulants also facilitate negatively motivated behaviour, such as Sidman shock-avoidance behaviour (Niemegeers et al., 1970a). Further, as shown for apomorphine (Broekkamp and van Rossum, 1974) facilitation or depression of self-stimulation occurs independently of the brain-site stimulated (see also Liebman and Butcher, 1973, 1974).

The above date suggest that CNS-stimulants activate a brain-system involved in both reward and avoidance. It was argued, quite justifiably (Stein, 1962a, 1964b), that amphetamine augments self-stimulation and avoidance, by virtue of lowering the thresholds in the hypothalamic incentive system. In this conception, reward and punishment interact reciprocally, both feeding into the motor system (Stein, 1964b). The self-stimulation substrate is then a reinforcement system involved in all kinds of operant behaviour.
Because drug-effects are independent of the electrode localization, the effects cannot be explained by an action of these drugs on the neurones activated by the stimulation. Further, the mainly noradrenergic hypothalamo-limbic system is hardly likely to be the only substrate for the observed effects. It is emphasized that the dopaminergic nigrostriatal system is a more likely candidate.
It has been established that striatal systems not only control motor functions (e.g. Cools, 1973). Overactivation of this system (for example by amphetamine) or nonphysiological receptor stimulation (for example by apomorphine) is disturbing. This confirms the concept that an intact DA nigrostriatal system, functioning within limits, is required for the expression of learned behaviour (Ungerstedt, 1971b). Finally, many of the features of the effects of CNS-stimulants fit into the hypothesis that the nigrostriatal system is a drive-induction system (Crow, 1976).

3.3. Cholinergics and anticholinergics

The role of acetylcholine (ACh) at the vertebrate neuromuscular junction (e.g. Eccles, 1964) is one of the best studied examples of chemical transmission. At the periphery, a distinction has been made between a «muscarinic» and a «nicotinic» type of receptor. The presence of cholinergic neurons in the brain is demonstrated by histochemical staining of the enzyme acetylcholinesterase. These neurons are widely diffused (Lewis and Shute, 1967 and Shute and Lewis, 1967). A central representation of both cholinergic systems, muscarinic and nicotinic, has been described by Bradley (1968). It is generally assumed that cholinergic systems play a modulatory role in various types of behaviour (Pradhan and Dutta, 1971), including self-stimulation (Olds and Domino, 1969a, b).

3.3.1. Cholinergics

Cholinergic muscarinic agonists exert response depressant effects on self-stimulation behaviour. With pilocarpine, the ACh analogue, RD was dose-related, peaking 20-30 min after injection (Newman, 1972). The cholinesterase inhibitor physostigmine induced a time- and dose-related RD (Newman, 1972; Olds and Domino, 1969a, b). Arecoline, a more peripherally acting cholinesterase inhibitor, also induced RD (Olds and Domino, 1969a, b; Pradhan and Kamat, 1972). The onset was short and recovery was quick. The quaternary ammonium neostigmine, acting mainly peripherally, was virtually without effect. (Jung and Boyd, 1966; Domino and Olds, 1968; Newman, 1972).

With nicotine, a ganglion stimulating agent, Olds and Domino (1969a, b) found a transient and variable RD, while other authors were able to demonstrate facilitation (Bowling and Pradhan, 1967), which was most prominent in low self-stimulators and which was related to time and dose (Newman, 1972).

3.3.2. Anticholinergics (Fig. 6)

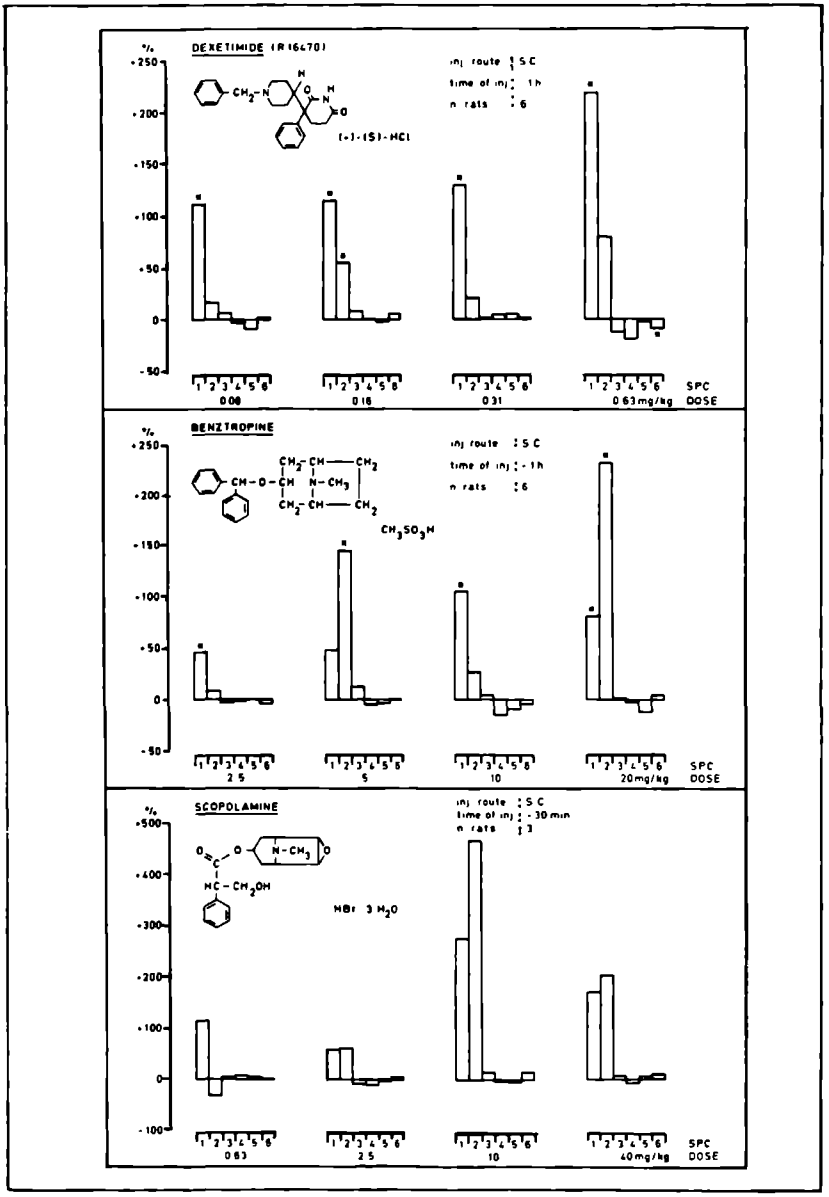
3.3.2.1. Dexetimide

Dexetimide induces a dose-related facilitation of self-stimulation. The RE is observed on the SPC's inducing low control response rates (SPC 1 and 2) and almost exclusively significant on SPC1. The lack of significant effects on other SPC's is mainly due to inter-individual variability. In 4 out of 6 rats RE is more pronounced than RD, but in 2 other rats RD predominates.

3.3.2.2. Benztropine

A rather irregular dose-response curve is obtained: RE is highest at SPC1 with 10 mg/kg of benztropine and at SPC2 with 40 mg/kg of benztropine. The RE is most pronounced at the low intensity SPC2, which contrasts with the observation that dexetimide causes a more pronounced RE at the low frequency SPC1. As with dexetimide, a slight RD is found at the other SPC's, but statistical significance is not reached. This, again is mainly due to inter-individual variability because RD predominates in 2 out of 6 rats.

Fig. 6: Response rates (all rats combined) in percentages of the respective control response rates, obtained with different doses (mg/kg) and for each stimulus parameter combination (SPC) with dexetimide, benztropine and scopolamine. Chemical structure, injection route, time of injection and number of rats tested are indicated at the top of the figure.



3.3.2.3. Scopolamine

The number of animals tested is small but the results indicate that scopolamine induces effects comparable to those found with dexetimide and benztropine. The dose-response curve is irregular. RE is highest with 10 mg/kg and lowest with 2.5 mg/kg of scopolamine. In 1 out of 3 rats, RD outweighs RE.

3.3.3. Conclusion

Muscarinic cholinergic agents mainly exert RD. The peripheral acting cholinergics do not change the self-stimulation rate. Nicotine, on the other hand, facilitates self-stimulation. Muscarinic anticholinergics induce peripheral and central effects (Janssen and Niemegeers, 1967). Relatively high doses of the anticholinergics are required to induce changes of self-stimulation rate. A central action is required since peripherally-acting anticholinergics, such as isopropamide, do not affect self-stimulation. The RE is not clearly dose-related, only observed during low base-line responding and the inter-individual variability is pronounced. The latter is responsible for lack of significance.

3.3.4. Discussion

Muscarinic agonists cause depression of self-stimulation. This is due to a central action, because cholinergics which do not cross the blood-brain barrier fail to change self-stimulation performance. Domino and Olds (1968) have shown that the depression of self-stimulation is associated with rise in the ACh-level. It could be expected that lowering the ACh-level, for instance by means of anticholinergics, would facilitate self-stimulation. It was subsequently confirmed that muscarinic antagonists chiefly produce response enhancement.

The effects on self-stimulation are probably not only due to an anticholinergic activity, since muscarinic anticholinergics also affect catecholamines. Scopolamine and benztropine increase the turnover of noradrenaline (NA) and decrease the turnover of dopamine (DA) (Corrodi et al., 1972). Benztropine and dexetimide also block the uptake of DA (Coyle and Snyder, 1969; Leysen, pers. comm.). The effects of anticholinergics on DA and NA are indirect and can be demonstrated most easily in those structures in which cholinergic neurones are supposed to interact with aminergic neurones, such as in the striatal structures. Such an interaction between dopaminergic and cholinergic neurones can be demonstrated behaviourally in experiments in which anticholinergics are shown to reverse the inhibition of self-stimulation produced by neuroleptics. The latter effect is assumed to be due to a blockade of DA-receptors (van Rossum, 1966, 1967; see further Chapter VII, section 7). The action of nicotine might also depend on NA, since depletion of NA, for instance by reserpine, prevents nicotine from facilitating self-stimulation. In order to obtain measurable effects on self-stimulation, high doses of the anticholinergics are required. As measured in the anti-pilocarpine test in rats (Janssen and Niemegeers, 1967), the ED_{50}-dose of central anticholinergic activity (e.g. tremor,

chewing) is obtained with 0.016 mg/kg of scopolamine, 0.080 mg/kg of benzetimide and 0.24 mg/kg of benztropine. The doses used in the self-stimulation experiments largely exceed the centrally active doses of the anticholinergics. So, the effects of the anticholinergics might not be due to an effect on ACh but on DA (or NA) via cholinergic neurons. This led to the question of whether a central muscarinic cholinergic system is functional during self-stimulation. The absence of significant changes on neuronal responses measured in various parts of the brain (hypothalamus, preoptic, cingulate and midbrain) after administration of anticholinergics, suggests that cholinergic systems modulate diffusely (Olds and Ito, 1973).

The type of modulation would be inhibitory. The concept inhibition plays an important rôle in the description of behaviour. Loss of inhibitory control has been shown in experiments in which various limbic structures were lesioned (e.g. McCleary, 1966).

Stein (1964b, 1967) assigned the inhibitory role in self-stimulation to the periventricular cholinergic system (which he termed «no-go system»). The ventromedial nucleus of the hypothalamus would be an important link in a cholinergic system mediating behavioural suppression (Margules and Stein, 1969). This system would interact with a facilitatory noradrenergic system (termed a «go-system»). Both systems would be mutually inhibitory and determine behavioural output. Such an interaction was shown in, for instance, experiments by Olds and Olds (1964) in which they described how stimulation in «aversive» brain areas, such as the tegmentum, significantly depressed self-stimulation.

Although the idea of a dual system feeding a final common pathway is interesting, there is little evidence for the cholinergic mediation of a suppressive system. It is not known whether «aversive» stimulation depressed self-stimulation merely by stimulation of cholinergic neurones or by some other means. The behavioural deficits occurring after lesioning limbic structures can be interpreted in terms of a loss of inhibitory control. However, lesions do not only affect cholinergic systems and it is hard to accept that a general cholinergic blockade interferes with all inhibition-related mechanisms (Grossman, 1972). Further, limbic structures do no serve identical behavioural purposes. Finally, findings on lesioning or locally administered cholinergics and anticholinergics cannot unequivocally be interpreted in terms of response modulation, Colpaert (1975) proposed that lesions of the ventromedial hypothalamus and of other limbic structures as well, caused a failure in the acquisition of fear as secondary drive.

On a hypothetical basis, one could assume that cholinergic systems are one source of inhibitory control, whereas other systems subserve adaptation to the environment by way of fear acquisition. These systems could modulate behavioural output and function in balance with aminergic transmitter systems sustaining self-stimulation.

3.4. Minor tranquillizers

Drugs which belong to the chemical group of the benzodiazepines, share

a variety of properties (Schallek et al., 1972; Zbinden and Randall, 1967). At lower doses hyperactivity can be observed, while at higher doses they cause sedation and EEG-deceleration. Chlordiazepoxide (Librium) and diazepam (Valium) are used as anti-anxiety agents whereas nitrazepam has sedative-hypnotic properties and is used as a «sleeping-pill».

3.4.1. Chlordiazepoxide (Fig. 7)

Chlordiazepoxide mainly facilitates self-stimulation, but no linear dose-relationship is found. RE is also pronounced at dose-levels (10 and 20 mg/kg) causing a pronounced disturbance of locomotor activity (named «ataxia»). RE is statistically significant at SPC1 and SPC2 (except with 5 mg/kg at SPC1). The very high RE obtained at SPC2 might particularly be due to a very low control response level. In addition, less sensitive self-stimulators (rats responding at low rates) are more susceptible to RE than rats which have higher control response levels. In all rats, however, RE exceeds RD.

In additional experiments (Wauquier, 1974), chlordiazepoxide was given to rats which could freely and continuously lever-press for brain-stimulation (SPC1). These rats lived in cages where the environmental conditions were kept constant. The rats self-stimulated at low rates but the self-stimulation activity showed a circadian rhythmicity. Chlordiazepoxide (10 mg/kg given orally) markedly enhanced self-stimulation in 3 out of 6 rats. Moreover, prolonged RE was found, exceeding direct drug effects.

3.4.2. Diazepam (Fig. 7)

RE as well as RD increase as the dose of diazepam increases. Simultaneously, a gradual, more pronounced disturbance of locomotor activity is observed. RE, however largely exceeds RD. The RE is most easily observed at low control base-line levels. The facilitation of self-stimulation is clearly dose-related, but the results fail to reach statistical significance at all dose-levels. This is especially due to the large variability with respect to drug-effects and especially because RD exceeds RE in one rat.

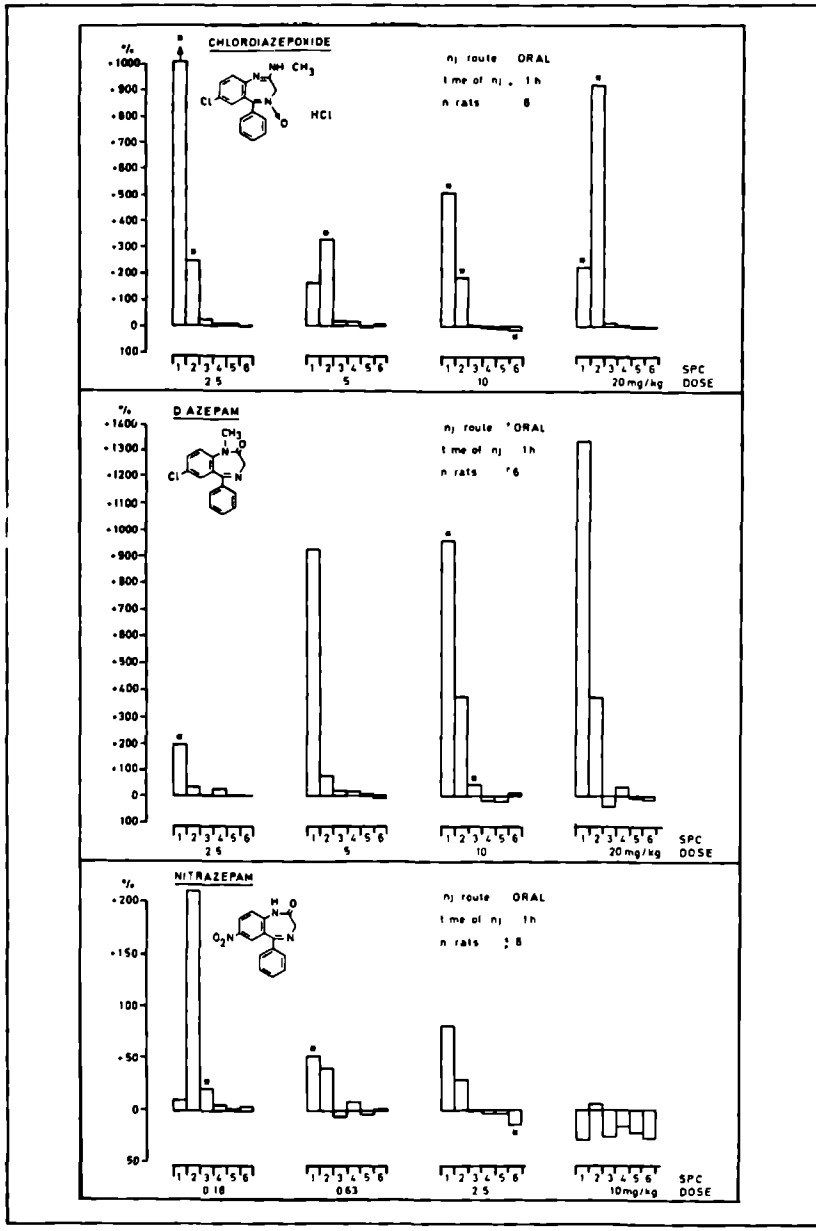
3.4.3. Nitrazepam (Fig. 7)

Nitrazepam causes a dose-related RD. With some doses RE is also observed. RE is far less pronounced than the RE induced by chlordiazepoxide and diazepam. Again, there is a large inter-individual variability. There is further no relation between RE and base-line responding obtained with each individual rat.

3.4.4. Conclusion

Chlordiazepoxide and diazepam preferentially induce a dose-related facilitation of self-stimulation, whereas nitrazepam causes more inhibition. The highest RE is found with chlordiazepoxide. All three compounds induce facilitation of low base-line responding. The inter-individual variability is pronounced. The doses > 5 mg/kg of chlordiazepoxide, > 2.5 mg/kg of diazepam and > 2.5 mg/kg of nitrazepam cause a

Fig. 7: Response rates (all rats combined) in percentages of the respective control response rates, obtained with different doses (mg/kg) and for each stimulus parameter combination (SPC) with chlordiazepoxide, diazepam and nitrazepam. Chemical structure, injection route, time of injection and number of rats tested are indicated at the top of the figure.



pronounced muscle relaxation (Desmedt et al., 1976) and induce disturbance of locomotor activity (ataxia).

3.4.5. Discussion

The slight depression of self-stimulation found with chlordiazepoxide and diazepam and the more pronounced inhibition induced by nitrazepam, might be related to the uncoordinated motor activity and sedation caused by these drugs. Corrodi et al. (1971) reported that benzodiazepines decrease the nervous activity in noradrenergic neurones, which could be related to the sedation and EEG-deceleration. At the dose-levels causing ataxia, the benzodiazepines protect against tonic and clonic seizures induced by pentylenetetrazol in rats (Desmedt et al., 1976). This characteristic explains their clinical usefulness in convulsive seizures in humans (e.g. Gastaut et al., 1965; Millichap and Ortiz, 1966). The muscle relaxation might, to a certain extent, contribute to the anti-anxiety effects, assuming that there is a reciprocal interaction between the vegetative peripheral nerve system and brain.

It is very unlikely that the anticonvulsant properties of the benzodiazepines explain the facilitation of self-stimulation. Convulsions are not very often associated with self-stimulation in the lateral hypothalamic area and anticonvulsant drugs such as baclophen, diphenylhydantoin, ethoxsuccimide and trimethadione do not enhance self-stimulation (unpublished observations). Olds (1966) suggested that chlordiazepoxide «primarily affected the reward system». If this is true, one might, for instance, wonder why the interindividual variability is so large. Panksepp et al. (1970), on the other hand, favoured the hypothesis that chlordiazepoxide facilitated self-stimulation indirectly, i.e. by counteracting an «aversive» system. These authors showed that chlordiazepoxide mainly increased self-stimulation from electrodes which also yielded reliable escape behaviour. Self-stimulation through such electrodes would be rewarding but also fear-inducing. Chlordiazepoxide might reduce this fear and consequently enhance self-stimulation.

Further, when stimulation is shifted to sub-threshold level, chlordiazepoxide prolongs responding in the extinction period (Gandelman and Trowill, 1968). The latter effect could be explained in terms of a counteraction of the aversion produced by non-reinforcement. It is not known whether chlordiazepoxide reduces the threshold for self-stimulation, which would also explain the facilitation.

Chlordiazepoxide did not facilitate the escape behaviour induced by aversive stimulation in the dorsal tegmental area (Olds, 1966) but facilitated escape from stimulation in hypothalamic areas (Panksepp et al., 1970). These contrasting findings might indicate that the inhibitory system on which benzodiazepines impinge is not cholinergic-mediated (dorsal tegmental reticular formation). It is more likely that facilitation of self-stimulation results from the inhibition of a serotonergic system running through the medial forebrain bundle. Moreover, Stein et al. (1973) presented evidence that the antianxiety action of benzodiazepines is due to a decreased activity in serotonergic neurones. It is likely that the

effects of minor tranquillizers on DA (and NA) are related to their sedative properties at high dose levels (Corrodi et al. 1971).
There is experimental evidence for the rôle of serotonin in self-stimulation. Stein (1971) showed that serotonin, given intraventricularly, suppressed self-stimulation. Poschel and Ninteman (1971) also postulated an inhibitory role of the serotonergic system in self-stimulation behaviour. Their interpretation is mainly based upon the facilitatory effects obtained with parachlorophenylalamine (PCPA), an inhibitor of the synthesis of serotonin. Results of PCPA-effects described by Stark et al. (1970), however, cast some doubt on the specificity of PCPA.
Beyond doubt is the fact that the inhibitory role of a serotonergic system is not related only to self-stimulation. PCPA for instance, also induced hyperphagia and obesity when given intraventricularly (Breisch et al., 1976). It is further known that stimulation in the raphe nuclei, from which serotonergic fibres originate, produces electroencephalographic sleep (e.g. Kostowski et al., 1969), whereas lesioning these structures produces extreme activation and sleepiness (Jouvet, 1974). Low frequency stimulation in the raphe nuclei (and in the lateral hypothalamic area as well) was shown to release serotonin in terminal forebrain structures (Kostowski et al., 1969). It could be argued that serotonin has not a suppressive influence on self-stimulation in the lateral hypothalamic area, since self-stimulation can also be obtained from electrode placements in raphe nuclei (e.g. Margules, 1969). It is, however, still a matter of debate whether raphe-self-stimulation is not due via activation of the locus coerulens, origin of the dorsal noradrenergic pathway. One might tentatively suggest that a serotonergic system originating in the raphe nuclei and running through the medial forebrain bundle, might have a suppressive influence on behaviour, including self-stimulation. Suppressing this system would for one thing, result in fear-reduction (Stein et al., 1973) and consequently facilitate behaviour. This is, most convincingly demonstrated in situations in which fear is probably causally involved in inhibition. Reward behaviour might be governed by two inhibitory systems: one which is cholinergic and not active during self-stimulation, another which is serotonergic, active during self-stimulation and mainly related to fear acquisition.

3.5. Narcotic analgesics (1)

Narcotic analgesics cause depression or facilitation which is species-, time- and dose-related. Some of these, such as morphine, are self-administered by animals, cause dependence and are abused in humans. The effects of fentanyl, piritramide and morphine were tested on self-stimulation. In additional experiments analgesic activity and catatonia were measured.
Analgesic activity was measured in the tail withdrawal test in rats (Janssen et al., 1963). Failure to withdraw the tail from water at 55°C

(1) The results of this investigation have already been published (Wauquier and Niemegeers, 1976a).

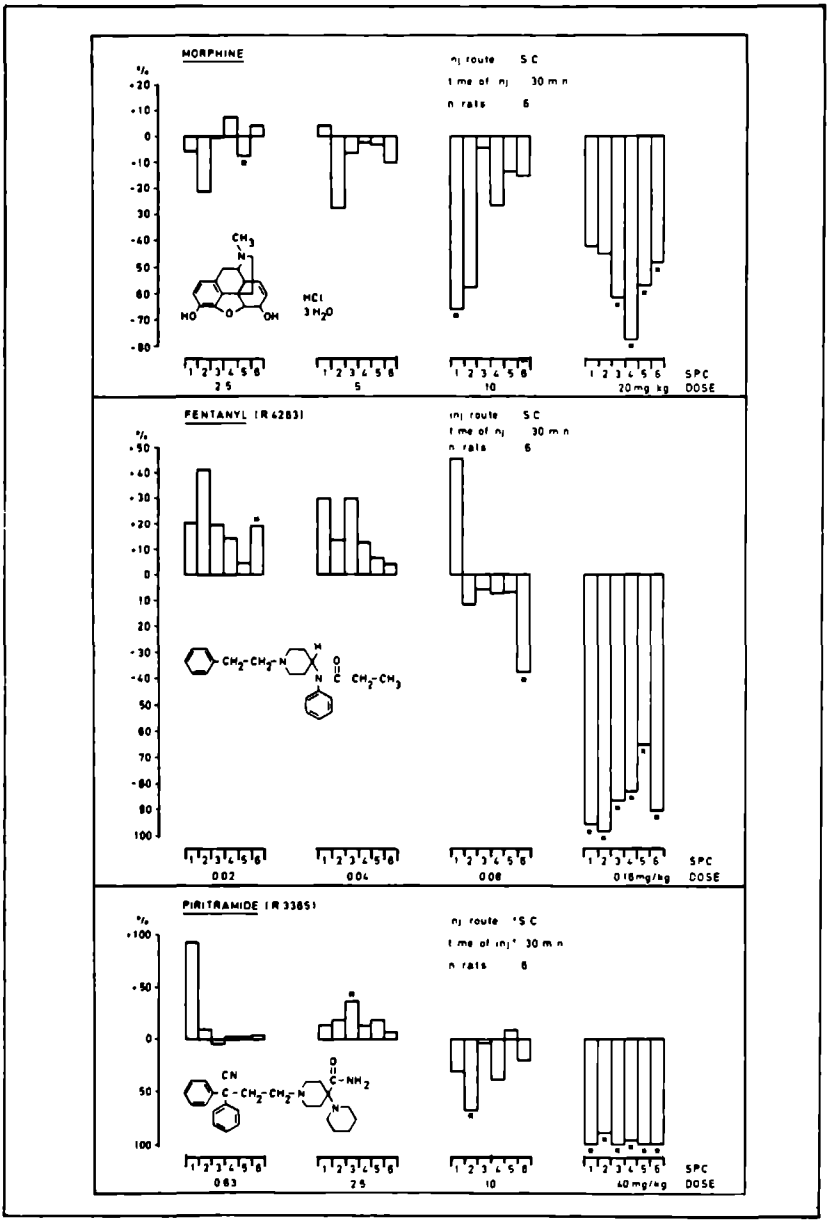
within 10 sec was used as the criterion for calculating ED_{50} values. Catatonia (muscular rigidity and loss of righting reflex) was assessed according to a scoring system described previously (Wauquier et al., 1974). Muscular rigidity was felt by hand grip and scored from o (no rigidity) to 3 (lead-pipe rigidity). For calculating ED_{50} values (mg/kg) score $\geqslant$ 2 (obvious rigidity) was adapted as criterion.

3.5.1. Morphine (Fig. 8)
With morphine a dose-related RD is found. The estimated ED_{50}-value of RD is 16.4 mg/kg. RD is most pronounced at the highest dose tested (20 mg/kg) and significant at the SPC's 3, 4, 5 and 6. At lower doses morphine slightly enhanced self-stimulation. The results fail, however, to reach statistical significance. There is no apparent relationship between RD and individual sensitivity of the rats to brain-stimulation.
At dose-levels inhibiting self-stimulation, morphine causes catatonia. The calculated ED_{50}-value of morphine-induced catatonia is 11.8 mg/kg (limits: 9.20-15.21). Analgesia is obtained at even lower doses, the ED_{50}-value being 7.86 mg/kg (limits: 6.82-9.06).
In another study (Wauquier et al., 1974 and see Chapter VII, section 7), it was shown that naloxone at a dose (5 mg/kg) which was ineffective on its own, reversed the morphine-induced inhibition (40 mg/kg) of self-stimulation, as well as the associated catatonia.

3.5.2. Fentanyl (Fig. 8)
Fentanyl, a potent analgesic (Janssen et al., 1963), causes a dose-dependent RD. The estimated ED_{50}-value of RD is 0.099 mg/kg. At the highest dose tested (0.16 mg/kg) RD is significant at all SPC's. At low doses RE exceeds RD, but this is only statistically significant at SPC 6 with 0.02 mg/kg of fentanyl. There is no direct relationship between drug-effect and individual sensitivity to brain-stimulation. At dose-levels inhibiting self-stimulation ($\geqslant$ 0.08 mg/kg) fentanyl causes catatonia, the ED_{50}-value of catatonia being 0.068 mg/kg (limits 0.053-0.088). Analgesia is obtained at 0.036 mg/kg (0.028-0.046) of fentanyl. In additional experiments it was found that with chronic administration of fentanyl (1 injection of 0.16 mg/kg of fentanyl per day, half an hour before the session), tolerance to the suppressive effects developed. However, it took several days or, in some rats, even weeks to obtain these effects. Furthermore, excitation and depression alternated in a seemingly random fashion.

3.5.3. Piritramide (Fig. 8)
Piritramide is a potent analgesic with unusual chemical features (Janssen, 1961). Piritramide causes a dose-related RD, the ED_{50}-value being 11.4 mg/kg. The RD is significant at all SPC's with the highest dose tested (40 mg/kg). RE exceeds RD at low dose levels, but statistical significance is only reached at SPC3 with 2.5 mg/kg. Catatonia is induced with 11.3 mg/kg (6.21-20.56) and the ED_{50}-value of analgesia is 5.67 mg/kg (4.42-7.28).

Fig. 8: Response rates (all rats combined) in percentages of the respective control response rates, obtained with different doses (mg/kg) and for each stimulus parameter combination (SPC) with morphine, fentanyl and piritramide. Chemical structure, injection route, time of injection and number of rats tested are indicated at the top of the figure.



3.5.4. Conclusion

The three narcotic analgesics described here induce a dose-related RD, which is most pronounced at the highest dose tested. At low doses or after chronic administration, RE is also observed. There is no direct relationship between the sensitivity to brain-stimulation in each individual rat and drug-induced RD or RE.

The doses effectively inhibiting self-stimulation are higher than those inducing catatonia (muscle rigidity and loss of righting reflex) and those causing analgesia (as measured in the tail-withdrawal test).

3.5.5. Discussion

The inhibition of self-stimulation produced by the three narcotic analgesics fentanyl, morphine and piritramide is not necessarily related to the rewarding value of brain stimulation, since the doses effectively inhibiting self-stimulation are much higher than those required for profound analgesia, obvious rigidity and loss of righting reflex. These observations indicate that inhibition of self-stimulation might be due to a non-specific catatonia-inducing effect and, thus, that it results from motor incapacitation. Further, response depression obtained after i.p. or s.c. injection of morphine (doses ranging from 5 to 20 mg/kg) appears equally well with electrode placement in the medial forebrain bundle, septal region and posterior and lateral hypothalamus. (Olds, 1959; Olds and Travis, 1960; Adams et al., 1972; Lorens and Mitchell, 1973).

The facilitation observed after narcotic analgesics depends on the dose and time of measurement after injection.

Tolerance to the suppressive effects of narcotic analgesics has been described (Adams et al., 1972; Lorens and Mitchell, 1973). The excitatory effects appeared earlier on the 5th day of administration. In the study reported here, facilitatory effects were also found after the acute administration of narcotic analgesics, although statistical significance was rather weak.

Glick et al. (1973) reported that morphine affected the «reward structures» involved in self-stimulation, which in turn altered the degree of dependence. Further, Marcus and Kornetsky (1974) reported that morphine reduced the threshold for self-stimulation. These findings might indicate that the facilitation obtained after administration of narcotic analgesics is due to a specific effect on structures underlying reinforcement of brain-stimulation. Moreover, it is well known that morphine is self-administered by different animals and abused by humans. We also showed that rats preferred to drink a solution of fentanyl + saccharine than to drink water + saccharine alone (Colpaert et al., 1976b).

The drug-induced increase of the excitability of reward pathways might be experienced as more rewarding, just as human beings experience these drugs as pleasurable. The increased activity of reward pathways might be responsible for drug-seeking behaviour (Collier, 1968; Marcus and Kornetsky, 1974). One might wonder, however, whether drug-seeking in addicts is not also avoidance behaviour for the anticipated unpleasurable withdrawal effects.

The sensitizing of the reinforcing substrate could be due to some altered biochemistry, but interpretation of this would be highly speculative. Some hypothesis related the effects of narcotic analgesics to their interaction with dopamine-receptors (Sasame et al., 1972, Broekkamp and van Rossum, 1975).
Finally, the most convincing effect of acute administration of narcotic analgesics on self-stimulation described here, is inhibition which was related to a non-specific catatonia-inducing effect.

3.6. Antidepressants

Nowadays three groups of antidepressants are used in medical practice: tricyclic antidepressants, some CNS-stimulants and MAO-inhibitors. This does not mean that chemically different compounds cannot possess antidepressant activity, for example, some antihistamines such as diphenhydramine and the anthelmintic tetramisole and its isomers. The antidepressants of the tricyclic type do not cause observable behavioural effects except at high doses and/or in combination with other drugs.

3.6.1. Desipramine (Fig. 9)

This compound was only studied in 3 rats. The main effect in RD, reaching -12.1 %, -15.9 % and -14.6 % in total (sum of the 6 SPC's) with respectively 2.5, 10 and 40 mg/kg. A small RE not exceeding control variability is observed. The inhibition is highest on the SPC's inducing low control response rates and vice versa. The highest RD is obtained with rat 3, for which the lowest control response rates were recorded.

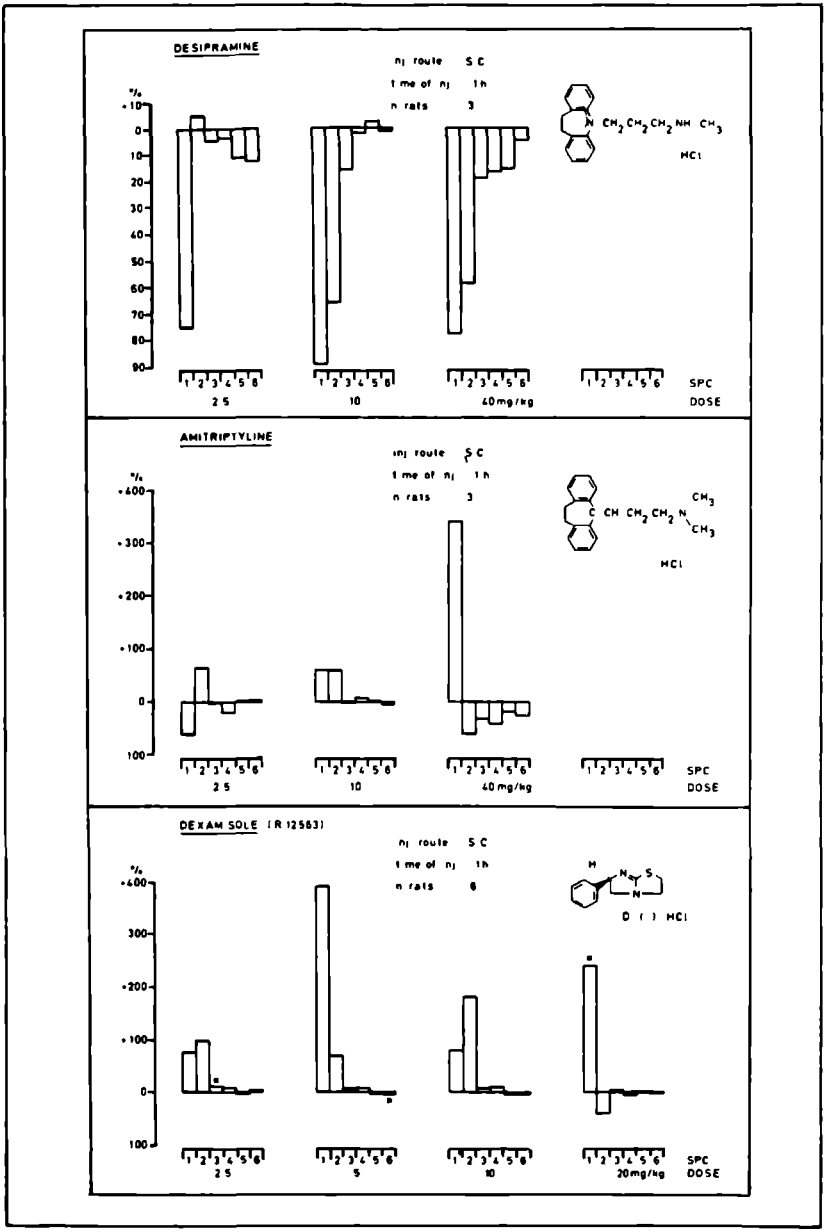
3.6.2. Amitriptyline (Fig. 9)

This compound was only studied in 3 rats. The doses 2.5 and 10 mg/kg cause only minor effects. Some RE is observed at SPC1 and RD on the other SPC's with 40 mg/kg, mainly due to the effects in one rat.

3.6.3. Dexamisole (Fig. 9)

Dexamisole is the d-isomer of tetramisole, a broad-spectrum anthelmintic (Thienpont et al., 1966). It was found that tetramisole (Brugmans et al., 1972) and both isomers levamisole (Deberdt, 1973) and dexamisole (Bobon et al., 1974) are of benefit in certain forms of depression. Bobon et al. (1974) reported that dexamisole was effective in 40 % of the tested patients with retarded depression. Side-effects, probably related to the doses and not reliably found in all patients, were tension, anxiety, tremor and some insomnia.
On self-stimulation, dexamisole induces RE at all doses tested. The dose-response curve is rather irregular. RE is most pronounced on SPC1 and 2, being significant only at SPC1 with 20 mg/kg. RD is rather small. In 5 out of 6 rats a preferential RE is observed, whereas RD is more pronounced than RE in one rat.

Fig. 9: Response rates (all rats combined) in percentages of the respective control response rates, obtained with different doses (mg/kg) and for each stimulus parameter combination (SPC) with desipramine, amitriptyline and dexamisole. Chemical structure, injection route, time of injection and number of rats tested are indicated at the top of the figure.



3.6.4. Conclusion

Desipramine preferentially causes RD, amitriptyline induces a slight RE and dexamisole causes a clear but not dose-related RE. It appears that the effects obtained with dexamisole are different from the tricyclic antidepressants. There are, however, individual differences between the rats with respect to drug-response, which are responsible for the lack of significance.

3.6.5. Discussion

Antidepressants only slightly affect spontaneous or conditioned behaviour. Their activity is mainly shown in situations where base-line activity is lowered or, by the potentiation of enhanced activity. An example of the former is the antagonism of reserpine (or analogues)-induced behavioural and peripheral phenomena in rats and mice, i.e. locomotor activity inhibition, hypothermia, miosis and ptosis (e.g. Colpaert et al., 1975a). An example of the latter is the potentiation of the effects of CNS-stimulants such as amphetamine-induced stereotypes in rats (e.g. Lew et al., 1971). Antidepressants would be expected to facilitate behaviour maintained by low reinforcement, such as the low control response rates induced by SPC1 and 2. In our experiments, tricyclic antidepressants cause minor effects or are depressing at high dose levels. This was also found in other experiments on conditioned behaviour (Cook and Kelleher, 1962). Only one report available in the literature describes facilitation of self-stimulation in cats obtained with imipramine (2-3 mg/kg) (Horovitz, 1962). No further experimental work has been done on this, possibly species-related, effect.

Tricyclic antidepressants potentiate the excitatory effects of amphetamine and cocaine on self-stimulation (Bénešová, 1969; Stein, 1967). This effect might be due to a retardation of the inactivation of released amines. The amphetamine-interaction is a metabolic interaction (Lewander, 1969) resulting in higher amphetamine levels in the brain. The pharmacological interaction consists, rather, of a prolongation of stereotypes and agitation induced with amphetamine.

Self-stimulation which according to Stein (1968), is mediated by NA is not, however, enhanced by tricyclic antidepressants, as would be expected on the grounds of potentiation of released NA during stimulation. This might be due to the α-adrenolytic activity obtained with some anti-depressants, usually at relatively high doses (Van Nueten, pers. communications). Dexamisole, on the other hand, facilitated self-stimulation. Recently, it was found that dexamisole potentiates the response to sympathetic stimulation, probably by stimulating sympathetic ganglia, and NA effects as well. The latter may be explained by inhibition of reuptake of NA (Vanhoutte and Van Nueten, 1975) and could be responsible for the observed effects.

Hypotheses on depression have been based on biochemical or pharmacobiological data. Janowsky et al. (1972) proposed a cholinergic-adrenergic hypothesis of mania-depression. This «balance-theory» was particularly based on the finding that some compounds, such as

iprindole, did not affect amines (Fann et al., 1972). Another type of theory was advanced by Stein (Stein 1962 a,b). He stated that depression is due to either a «hypoactive» reward system (passive or primary depression) or an overactive punishment system (active or secondary depression). The main point in this concept is that depression is due to a disordered functioning of the reward system. The idea that behaviour should be governed by two antagonistic systems: one responsible for aversion, withdrawal, punishment, and one responsible for approach and reward is far from being new (see for example Van der Staak, 1975). Undoubtedly, other systems may also modulate the reward system (see previous sections). Both mechanisms would be active when an organism is presented with a stimulus. The hedonic value would then be determined by the stimulus intensity.

Berlyne (1960) extended this concept by relating hedonic value to arousal potential, the latter being determined by specific stimulus properties. This differs from Hebb's concepts (Hebb, 1955) in which hedonic value depends on the level of arousal. Berlyne (1973) further stated that hedonic value can result from either reducing or enhancing arousal (termed respectively «arousal reduction» and «arousal boost»).

These ideas correlate with Olds' and Olds' (1965) scheme of interacting brain systems governing hedonic processes, except that these authors postulate a third positive reinforcement focus, located in the lateral hypothalamic region.

Stein's hypothesis is, although interesting, an over-simplification. The advantage is that it might be a starting point for advancing experimental models. One which we developed consisted of using a progressive (each 2 min) increasing fixed ratio (FR) schedule (up to 9 responses for 1 stimulation) of brain-stimulation reinforcement, during sessions of 3 consecutive 20 min periods. Such a schedule resulted in a progressive increase of self-stimulation (up to FR 3:1), followed by decreased responding (up to FR 5:1) and a still further decrease to operant level. During the last 2 min of each period a continuous reinforcement schedule (CRF, 1:1) was applied. The rats were automatically given 1 stimulation at the start of the CRF. This resulted in an immediate revival of self-stimulation. This type of schedule might be a «model» of depression, since increasing the effort to obtain stimulation (increased FR) resulted in a drop of responding. Anthropomorphically stated, the effort became too much for the little reward achieved, rats became «depressed». Preliminary experiments with antidepressants indicated that responding was maintained for longer periods (or higher FR) than during control sessions.

The drawback of this type of experiment is that variability in control sessions is rather large (maybe reflecting «internal state») such that enhancement after drug-treatment as compared to control is not extremely pronounced. Changes in procedure might result in a better stability of control responding. The creation of a model of a human disease in rats, however, is still very much a matter of speculation, but a valid approach consists of translating fundamental symptoms into experimental terms.

3.7. Hypnosedatives

Hypnosedatives cause minor behavioral effects at low dose levels; at higher doses they produce ataxia (uncoordinated locomotor activity); at still higher doses they induce hypnosis (sleep). At the dose-levels producing hypnosis they protect against convulsions induced by pentylenetetrazol. The effects of a non-barbiturate, etomidate, methohexital and pentobarbital are described.

3.7.1. Etomidate (Fig. 10)

Etomidate is a novel, non-barbiturate and fast-acting compound (Janssen et al., 1971, 1975b). It produces EEG-effects quite similar to those of the barbiturates such as methohexital, but has no undesirable cardiovascular side-effects (Wauquier et al., 1976b). On self-stimulation one observes very slight RE and KD with the 3 lowest doses tested (0.16, 0.63 and 2.5 mg/kg). At the highest dose tested (10 mg/kg, s.c.), RD is virtually complete and significant at SPC3, 4, 5 and 6. The RD is nearly equal at all SPC's except SPC1. In all rats RD is more pronounced than RE.

3.7.2. Methohexital (Fig. 10)

Methohexital is a barbiturate inducing hypnosis at doses approximately 7 times higher than obtained with etomidate. EEG-effects are similar to those obtained with etomidate, but the drug causes tachycardia and frequently apnea (Wauquier et al., 1976b). Methohexital was only tested on three rats for self-stimulation. At the dose-range tested RD is only small, RE is also observed at low control response rates.

3.7.3. Pentobarbital (Fig. 10)

Pentobarbital was only tested in three rats. Mainly RD is found and with one dose (10 mg/kg) RE on SPC1. The highest dose tested (20 mg/kg) causes a pronounced RD but the effects are quite variable on the different SPC's. In the three rats RD outweighs RE.

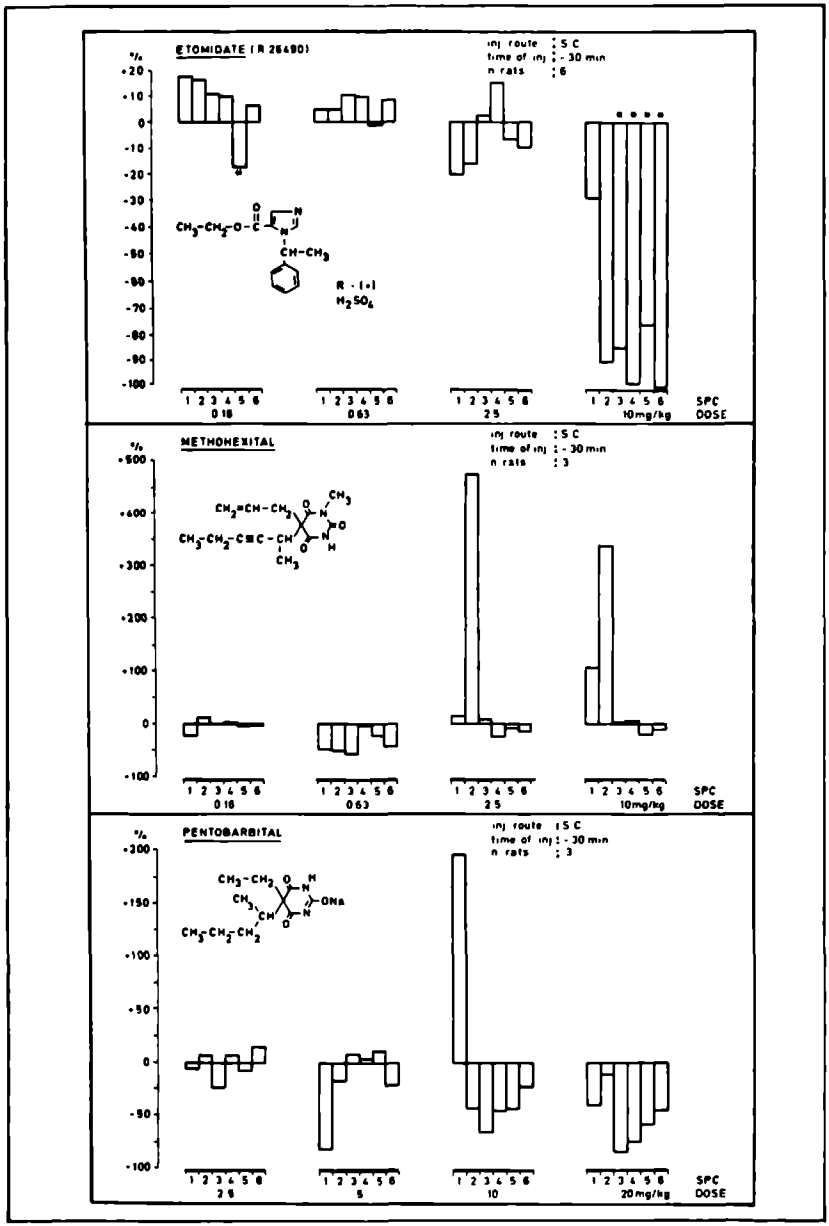
3.7.4. Conclusion

Hypnosedatives cause unspecific effects on self-stimulation, inhibit self-stimulation at dose levels inducing hypnosis. The unspecificity of the effects is best illustrated with etomidate, which at the highest dose tested produced almost the same RD at all SPC's.

3.7.5. Discussion

It is quite clear that hypnosedatives only affect the performance level, since they only moderately change self-stimulation, whereas high doses completely inhibit self-stimulation performance. The inhibition is unspecific, because, at these high doses, rats are under hypnosis and are therefore unable to press a lever. The drugs can therefore be discussed in terms of their interference with performance ability. They might be explained by their interference with the ascending reticular formation, this system determing consciousness and organization of motor patterns (Routtenberg, 1971a).

Fig. 10: Response rates (all rats combined) in percentages of the respective control response rates, obtained with different doses (mg/kg) and for each stimulus parameter combination (SPC) with etomidate, methohexital and pentobarbital. Chemical structure, injection route, time of injection and number of rats tested are indicated at the top of the figure.



They may also affect the cortex, as postulated by Doenicke et al. (1973) for etomidate, thus causing a disinhibition of subcortical structures.
Some hypnotics cause excitatory effects and induce an EEG-picture resembling an epileptic seizure. The excitatory effects might be a reason why certain barbiturates are abused. It appears, however, that barbiturates are abused not because they facilitate reward, but as a flight into unconsciousness.

3.8. General discussion

Self-stimulation is a particular kind of behaviour, i.e. caused by pathologically induced neuronal processes (Olds, 1973), through stimulation of implanted brain electrodes. Self-stimulation is sustained by positive reinforcement. Reinforcement is «In essence, this system involved in bridging the gap between behaviour and its physiological consequences.» (Valenstein, 1966, p. 158). The description of the self-stimulation phenomenon and its anatomical distribution suggested that the substrate of «immediate reinforcement» was detected. The concept «immediate reinforcement» was introduced by Valenstein (1966, 1970) to stress the independence of feedback from the physiological consequences of the behaviour and referred to the direct elicitation of the reinforcement process whether triggered by exteroceptors or interoceptors. This means that drive-reduction is only one source of reinforcement, which cannot account for reinforcement of direct brain stimulation. This does not exclude drives to action, such as gating behaviour. The hedonic value of the stimulation could, according to Berlyne (1973), be determined by increments or decrements of arousal potential, which covers all stimulus properties. Reinforcement could be activated by some complex changes in the activity of the underlying substrate. In self-stimulation then, situational factors, experimental paradigms and gating mechanisms (cues depending on internal states) codetermine the final output. Further, brain-stimulation, especially in certain structures such as the lateral hypothalamus, activates not only neuronal fibres mediating reward. Other modulating (inhibitory, fear-inducing) systems may be activated simultaneously.
The study of the influence of psychoactive drugs on brain self-stimulation is not only indicative for central drug-effects (Grossman, 1967, p. 284) but could help to elucidate which brain systems are involved and how they interact in the mediation of observed behaviour. Undoubtedly, drugs injected systemically have multiple actions. The following list is not even exhaustive. Drugs could change self-stimulation by affecting performance, reward, reinforcement, sensorimotor integration, retrieval; drugs may induce state-dependent effects or act as cues (see Colpaert et al., 1976a), etc. The main point discussed here, is that drugs influence self-stimulation through an action on performance or reinforcement, regardless of the particular motivation involved and further, through an action on modulating systems functioning in balance with transmitter systems underlying brain self-stimulation.

Some of the drug-effects can be discussed in terms of drug-interference with the performance ability, such as those obtained with hypnosedatives, high doses of minor tranquillizers or narcotic analgesics. The effects of these drugs are unspecifically related to reinforcement or reward. Obviously, hypnosedatives completely inhibit self-stimulation at dose-levels inducing hypnosis. Narcotic analgesics, at least when they are acutely administered at sufficiently large doses, inhibit self-stimulation by causing motor incapacitation (catatonia: muscle rigidity and loss of righting reflex). High doses of minor tranquillizers (and to a certain extent also tricyclic antidepressants) cause sedation and/or uncoordinated locomotor activity. These drugs, therefore, might inhibit self-stimulation by an action on motor systems and interfere with the ability to perform. High doses of CNS-stimulants which cause stereotype behaviour, also decrease performance. However, in this case, rats are able to perform since they even press the lever when brain-stimulation is no longer supplied (during «extinction»). The inhibition caused by these drugs is for a large degree due to a competition between goal-directed movements and stereotype behaviour, not related to lever-pressing. Self-stimulation at equal rates for different SPC's and the failure to extinguish after stimulation has been cut off, cannot be explained by the same mechanism. The performance of such rats is more like the performance of rats extensively lesioned in forebrain structures (Huston and Ornstein, 1976), which show a failure to habituate. It appears, therefore, that the high doses of CNS-stimulants cause a «functional lesion» interfering with the physiological activity of self-stimulation substrate systems.

CNS-stimulants are self-administered by animals and some are abused in humans. They appear to have reinforcing properties of their own, the physiological consequences being experienced as rewarding.

The mechanism accounting for the facilitation of self-stimulation might consist of a sensitizing or threshold-reduction of the reinforcement substrate. The failure to extinguish, however, might be due to a shaping of stereotype lever-pressing and to a lack of habituation non-relevant stimuli since brain-stimulation reward is lacking. Alternatively, one could assume that the interaction with the environment itself becomes rewarding (see for example Nuttin, 1973) or reflects a sustained anticipation.

The facilitation of self-stimulation seen after CNS-stimulants and acute or chronic administration of narcotic analgesics, might be due to a sensitization of the reinforcement substrate or to threshold-reduction.

Sensitization is a difficult concept to handle, since there is no evidence that the biochemistry of the system has been chronically affected. In addition, when administering drugs chronically, one probably has to take state-dependent effects into consideration, i.e. where making or not making a response is conditional upon a given drug (Colpaert et al., 1976a). Effects conditional upon the chronic administration of a drug can be shown, but these depend on stimuli associated with drug-administration rather than the drug itself. State-dependent effects associated with a given drug could play a rôle in drug-induced performance changes of self-stimulation. In order to demonstrate the involvement of these

effects, specific experiments are required to show that there is a lack of transfer to the no-drug condition and experiments in which similar or different drugs are substituted for the training drug.
It is conceivable that the effects obtained with lower doses of CNS-stimulants and narcotic analgesics are due to a specific effect on reinforcement. Reward could increase by threshold-reduction. This implies that stimulation which is not rewarding gains rewarding properties. Further, self-stimulation performance could increase for stimulation which is moderately rewarding. It might be questioned, that these drugs specifically affect reward, since similar enhancement of responses, aimed at escaping or avoiding aversive stimulation, such as electrical shock, is observed after the administration of these drugs (see Niemegeers et al., 1969a, b 1972).
Common to both reward and aversion in an operant behavioural situation, is the occurence of a reinforcing process. Both mechanisms interact with each other (Stein, 1964b) and feed into motor mechanisms, determing final output. These considerations imply that the «reward system» plays an important rôle in avoidance behaviour. Olds (1962) suggested, for instance, that chlorpromazine inhibited self-stimulation by virtue of an increase of the hypothalamic incentive system (see further Chapter VII). CNS-stimulants and narcotic analgesics may act by the opposite mechanism, i.e. decrease the threshold of the reinforcing system involved in both reward and aversion.
These considerations also imply that it is impossible to discuss «reward» without taking into consideration other mechanisms which modulate the former. From a pharmacological point of view, it is difficult to explain the effects obtained with cholinergics, anticholinergics and minor tranquillizers only on the basis of an impact on DA- or NA-systems, substrates of self-stimulation. Cholinergic and serotonergic systems probably function as systems involved in behavioural suppression on the one hand, and as systems involved in fear-induction on the other hand. The interaction is demonstrated by the fact that cholinergics at high doses, suppress self-stimulation, which is normalized by anticholinergics, which themselves, also at high doses enhance self-stimulation. Further, the action of nicotine might depend on the NA-system.
The inhibition seen after cholinergics suggests that the cholinergic network mediates behavioural suppression. This is further extensively described by Pradhan and Dutta (1971). It is unlikely, however, that the «aversive» system is only cholinergic-mediated and that all inhibition-related mechanisms are cholinergic.
The interaction between reward and aversion is also demonstrated by the fact that chlordiazepoxide facilitated self-stimulation primarily in those rats also showing escape behaviour. Since the activity of minor tranquillizers is regarded as being due to their influence on a serotonergic system, one could assume that escape is mediated through such a system. In view of the anti-anxiety effects of these drugs, one could argue that fear-reduction is causally related to the facilitation found and further, that the system mediating this is serotonergic. Again, one cannot state that all serotonergic systems are involved in mediating fear.

In conclusion: Psychoactive drugs change the self-stimulation activity by affecting the performance ability or by interfering with reinforcement. The latter is independent of the particular motivational state involved. Similar changes can be found on behaviour sustained by positive or negative motivation.
It is not clear whether certain drugs specifically alter reward, but one should not exclude such a possibility.

Chapter VII. Neuroleptics and brain self-stimulation (1)

INTRODUCTION

The question of which neuronal pathways are involved in self-stimulation behaviour and what rôle they play in the different aspects of this behaviour, has been the subject of a large number of studies (Wauquier and Rolls, 1976). The reinforcing properties of electrical stimulation of particular neuronal pathways must in some way be related to the activation of these pathways, caused by the electrical stimulation.

Pharmacological studies on self-stimulation and neurochemical identification of the pathways involved gave rise to the so-called catecholamine-hypothesis of self-stimulation behaviour (Crow, 1972; Dresse, 1966; Stein, 1968). According to this hypothesis the effects of electrical self-stimulation are mediated by noradrenergic and dopaminergic neuronal pathways. It has been shown, however, that self-stimulation behaviour can also be induced by applying electrical stimulation to non-aminergic structures (e.g. Liebman and Butcher, 1974). Moreover, there are controversies with regard to the functional rôle of the different aminergic structures in self-stimulation behaviour.

There are a variety of neuroleptics belonging to different chemical classes: the rauwolfia alkaloids (reserpine-like), the phenothiazines (chlorpromazine-like), the butyrophenones (haloperidol-like) and the diphenylbutylamines (pimozide-like). Particular attention has been directed towards neuroleptics which effectively control psychotic symptoms, reduce relapse and which enable patients to be reintegrated into society. Some neuroleptics are of benefit in neurotic or psychosomatic disorders; most of the neuroleptics, however, lack any beneficial effect on affective disorders.

Because neuroleptic drugs are specific and potent dopamine-receptor blocking agents (van Rossum, 1966), their inhibitory effect on self-stimulation appears consistent with a dopamine-hypothesis of self-stimulation. It could be argued that the inhibition is not specific for self-stimulation behaviour, and that the self-stimulation inhibition may be a simple consequence of impaired motor activity or may be due to a motivational deficit. The alternative hypothesis is that neuroleptics cause self-stimulation inhibition by interfering with sensorimotor integration. The latter is mediated partly via the dopaminergic nigrostriatal system.

(1) This chapter is based on Wauquier (1976b).

2. THE INVOLVEMENT OF DOPAMINE IN BRAIN SELF-STIMULATION

The evidence for an involvement of catecholaminergic (CA)-systems was extensively reviewed by German and Bowden (1974). They studied the degree of overlap between CA-systems (Ungerstedt, 1971a) and the distribution of anatomical sites supporting self-stimulation (e.g. Olds and Olds, 1963; Routtenberg and Malsbury, 1969). (1)

The following systems are now considered as substrates for self-stimulation: the dorsal noradrenergic system, originating in the locus coeruleus and running through the medial forebrain bundle (MFB) at the posterior hypothalamic level, through the basal forebrain and terminating in the amygdala, hippocampus and cortex; the nigrostriatal dopaminergic pathway and the mesolimbic dopaminergic pathway.

There have been discussions as to whether the ventral noradrenergic system originating in medullar nuclei A1, A2 and A5 and joining the MFB with the other CA-systems, was implicated or not (Arbuthnott et al., 1970; Clavier and Routtenberg. 1973, 1974).

Briefly, the involvement of dopaminergic systems in self-stimulation has been substantiated by anatomical studies, utilizing implanted electrodes, the brain lesion technique and pharmacological tests. Firstly, self-stimulation can be elicited when electrodes are placed in the cell bodies of the nigrostriatal pathway (Anlezark et al., 1973a, b; Crow, 1971, 1972; Routtenberg and Malsbury, 1969). Self-stimulation can also be obtained from the substantia nigra in dogs (see further: 5.2). In such dogs self-stimulation was associated with pronounced contralateral turning of the head and the trunk (which might indicate unilateral dopaminergic activation, Ungerstedt, 1971a).

Dresse (1966, 1967) described self-stimulation obtained from placements dorsal to the interpeduncular nucleus, where the cell bodies of the mesolimbic pathway are localized. Lesioning of these structures resulted in a diminution of noradrenergic (neocortex, gyrus dendatus, septum and preoptic area) and dopaminergic (olfactory tubercle and nucleus accumbens septi) terminals. Belluzi et al. (1975) explained self-stimulation resulting from the substantia nigra placements as being due to activation of a noradrenergic system passing in the vicinity of the electrodes. However, these experiments do not exclude an involvement of dopaminergic structures.

It has been shown that the cell bodies, the neuronal pathway, as well as the terminal sites of the DA nigrostriatal system, are able to support self-stimulation (German and Bowden, 1974; Routtenberg and Malsbury, 1969). Prado-Alcala et al. (1975) obtained self-stimulation from the substantia nigra to the entopeduncular nucleus, but not further. It could be argued that the lack of self-stimulation beyond the entopeduncular nucleus was due to stimulation of an insufficient number of fibres. However, in spite of these negative results there are other

(1) Anatomical and biochemical mapping studies are extensively described in Wauquier and Rolls (1976).

reports of self-stimulation in the caudate nucleus (Phillips et al., 1976; Routtenberg, 1971b and unpublished observations in dogs), and species-dependent effects could be involved (Justesen et al., 1963; Porter et al., 1959).
Secondly, lesion studies revealed the importance of the DA-systems as substrates for self-stimulation. Lesioning the substantia nigra or caudate nucleus produced drastic effects on behaviour in general (Mitcham and Thomas, 1972). Lesioning of the CA-pathways brought about by the intracerebral administration of 6-hydroxydopamine (6-OHDA) suppressed self-stimulation in addition to other behavioural responses (Breese et al., 1971; Stein and Wise, 1971). The local administration of 6-OHDA poses some methodological problems since, at the doses used, this agent lacks specificity and may effectively reduce concentrations of NA as well as of DA (E.g. Breese and Taylor, 1970).
Thirdly, the role of the DA-systems has been substantiated by the administration of drugs interfering with synthesis and release of DA. α methyl-paratyrosine (α-MPT), which causes a functional depletion of CA, depressed self-stimulation (Black and Cooper, 1970; Cooper et al., 1971; Liebman and Butcher, 1973) in the lateral hypothalamic area and in the ventral tegmental area. This was reinstated by L-dopa, which repletes cerebral DA (Stinus and Thierry, 1973) but also by NA (Ritter and Stein, 1973).
L-dopa itself increased self-stimulation when given together with a peripheral dopa-decarboxylase inhibitor. This is not antagonized by phenoxybenzamine but is by haloperidol (Kadzielawa, 1973). Liebman and Butcher (1973) found that L-dopa actually depressed self-stimulation behaviour, but that this was reinstated by doubling the current.
These experiments implicate an involvement of both amines, DA and NA.

Fla-63, an inhibitor of the synthesis of NA, caused a complete suppression of self-stimulation which was associated with a decrease in NA (Stinus et al., 1973). Wise and Stein (1969) found that this induced suppression could only be reversed by the application of l- or dl-NA and not by DA. Lippa et al. (1973), however, did not find that Fla-63 caused any significant effect on self-stimulation.
These discrepancies could be a consequence of the doses used, the administration schedule, the time of measurement and so forth. More important is the question of whether one is dealing with specific or unspecific behavioural effects. Rolls et al. (1974a) showed that disulfiram caused a moderate reduction in self-stimulation which was associated with drowsiness and Roll (1970) described that replacement of the sedated rats on the lever resulted in an immediate revival of self-stimulation. Similarly, Liebman and Butcher (1973) demonstrated that doubling the current resulted in active self-stimulation in a similar situation.
It can be concluded that there is evidence that self-stimulation is also induced from DA-structures, particularly those of the nigrostriatal

system. The pharmacological studies are less conclusive, but do emphasize problems in interpretation of the functional rôle of the DA nigrostriatal system in self-stimulation. The neuroleptic-induced effects on self-stimulation may be an additional means of defining this functional rôle in view of the fact that these drugs are potent dopamine-receptor blockers (van Rossum, 1966, 1970). In addition, selective NA-blockers and NA-agonists may be of importance in the further elucidation of the rôle of NA in self-stimulation behaviour. This is of importance since, according to recent experiments, DA- and NA-systems may mutually interact (Stephens et al.,1976).

3. THE INFLUENCE OF NEUROLEPTICS ON SELF-STIMULATION

Shortly after the discovery of self-stimulation, Olds and co-workers tested the influence of chlorpromazine and reserpine (e.g. Olds et al., 1957). These drugs were found to be powerful inhibitors of self-stimulation behaviour. However, site-dependent effects were apparent and self-stimulation in the posterior hypothalamic area was more susceptible to the disruptive effects of these agents than the other sites tested.
Dresse (1966, 1967) described the effects of larger groups of phenothiazines and butyrophenones and related the effects obtained on self-stimulation to a biochemical substrate.
In recent years some butyrophenones (haloperidol, spiroperidol) and the diphenylbutylamine pimozide have been tested more extensively, but the number of neuroleptics tested still remains limited. In addition, no comprehensive data on the characteristics of the inhibition obtained with neuroleptics and consequently, the nature of the inhibition, has been formulated. The aim of this section is to describe the influence of a large group of neuroleptics on self-stimulation.

3.1. Methods

A detailed description of the experimental animals, their housing conditions, surgery, electrical stimulation and the general set-up of the experiment has already been given in chapter IV. The procedure, followed in this investigation, is identical to that described in chapter VI. In all, 20 neuroleptics belonging to different chemical groups (Fig. 1) were investigated with respect to their effects on self-stimulation behaviour. 19 neuroleptics were tested on groups of 6 rats and one neuroleptic (droperidol) on a group of 3 rats. Four doses of each compound were given, the lowest during the first week and progressively higher doses on subsequent weeks. The neuroleptics were administered either subcutaneously or orally with one exception: pimozide. This compound was administered orally to a group of 6 rats and subcutaneously to another group of 6 rats. As was the case in the investigation described in chapter VI, saline was given on Tuesdays and drugs on Thursdays. The long-acting neuroleptics clopimozide, penfluri-

dol and pimozide (orally), however, were given on Monday sessions. Saline sessions preceded drug-treatment and recovery to control level occurred within one or two weeks after each dose.
The figures showing the drug-effects are presented in the same way as in Chapter VI: they represent the response rates obtained with all rats at each SPC and after each dose of a neuroleptic during the drug session (fourth day of the week, except for the long-acting neuroleptics clopimozide, penfluridol and pimozide - given orally - for which the first day was taken). They are expressed as percentages of the control response rates obtained during the control session (second day of the week, and fifth day for clopimozide, penfluridol and pimozide). Significant ($p < .05$) differences are indicated by an asterisk (Wilcoxon matched-pairs signed-ranks test, one-tailed probability).
Additional statistical tests are described in subsequent sections.

3.2. Results

The effects of the neuroleptics described have been reported very briefly by Wauquier (1976a) and some of the neuroleptics more extensively by Janssen et al. (1975), Wauquier and Niemegeers (1972, 1975, 1976b, c). Because the profiles of the neuroleptics tested are quite similar, it was not considered necessary to discuss each one separately.

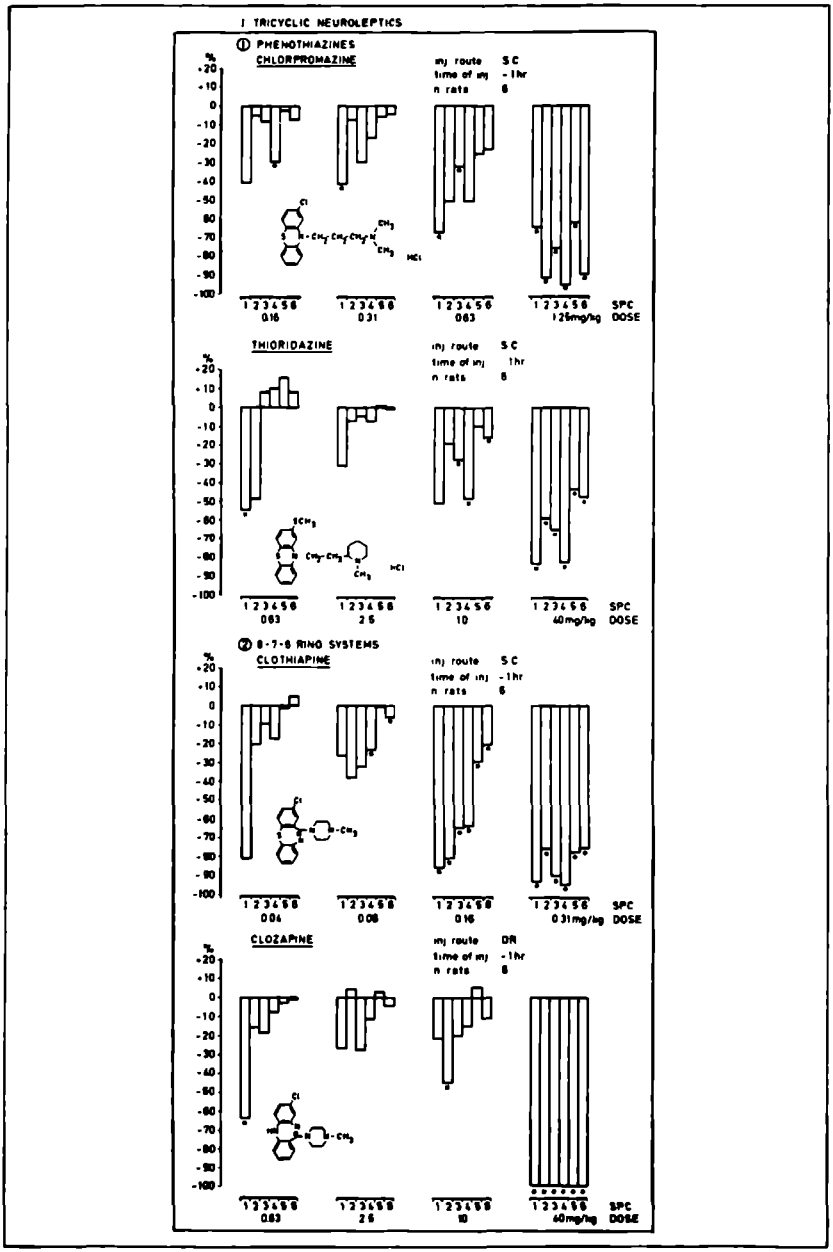
3.2.1. General description

Fig. 1a-f shows the percentage of lever-pressing as compared with the control response rates, obtained with each of 4 doses of the 20 neuroleptics and at each of the 6 SPC's.
All neuroleptics caused pronounced response inhibition and only slightly enhanced the response rates. The total response inhibition (effects on the one hour session, i.e. sum of the 6 SPC's) ranges from 24 % (thioridazine) to 65 % (pimozide, orally given). The inhibition is dose-related, ranging from a dose which is almost ineffective, to a dose causing almost complete suppression of self-stimulation. It appears that the response inhibition is inversely related to the base-line responding.

3.2.2. Dose-effect relationship

Fig. 1a-f shows dose-effect relationship. The Wilcoxon matched-pairs signed ranks-test, one-tailed probability, was used as a test for the significance of differences between drug- and control response rates. Significant effects ($p < .05$) are indicated by an asterisk.
All neuroleptics tested inhibited self-stimulation in a dose-dependent way. The dose-dependent decrease of self-stimulation obtained after some of the neuroleptics described here, has been observed in different situations and with different electrode localizations (Dresse, 1967; Kadzielawa, 1973, 1974; Liebman and Butcher, 1973, 1974; Olds and Olds, 1964; Olds and Travis, 1959, 1960; Phillips et al., 1975; Rolls et al., 1974b; Stark et al., 1969) (See Chapter III). The inhibition, however, is clearly base-line dependent.

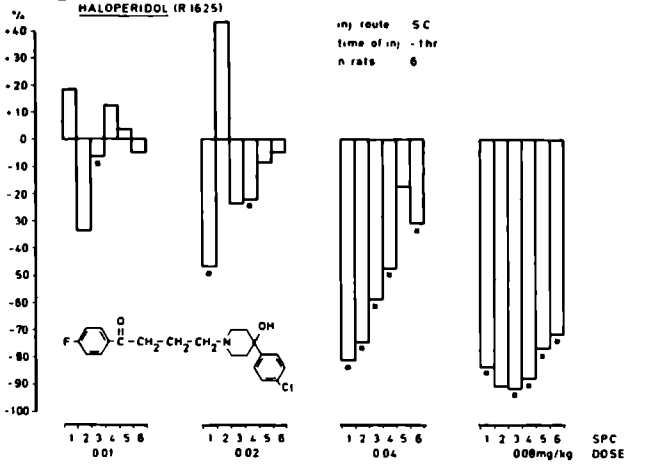
Fig. 1a-f: *Self-stimulation response rates in relation to control response rates, obtained with each of the 4 doses of 20 neuroleptics on each of the 6 SPC's. Asterisks indicate significant difference ($p \ll .05$) as compared to control (for details see Methods).*



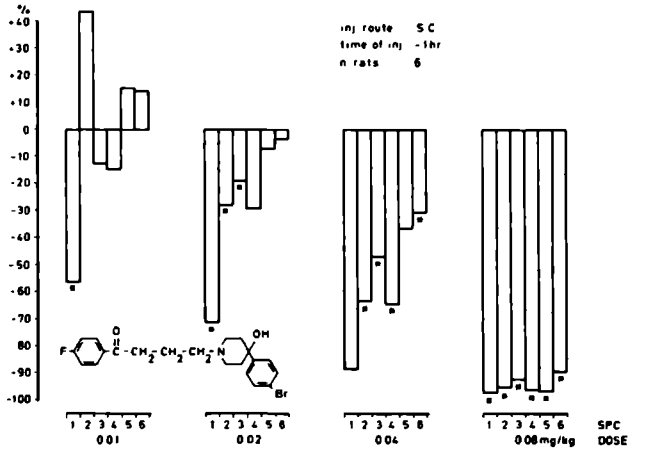
II BUTYROPHENONES

① 4 PHENYL – PIPERIDINO

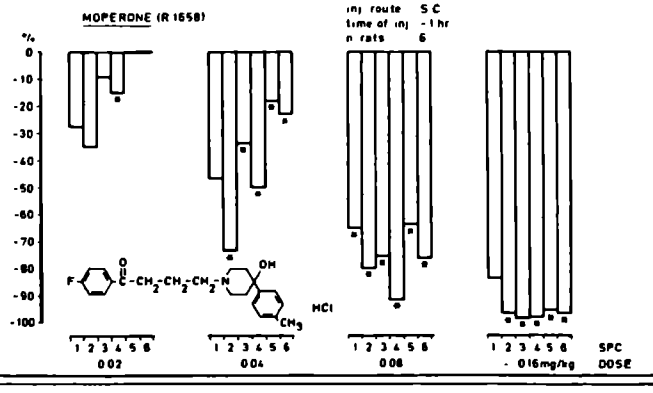
HALOPERIDOL (R 1625)

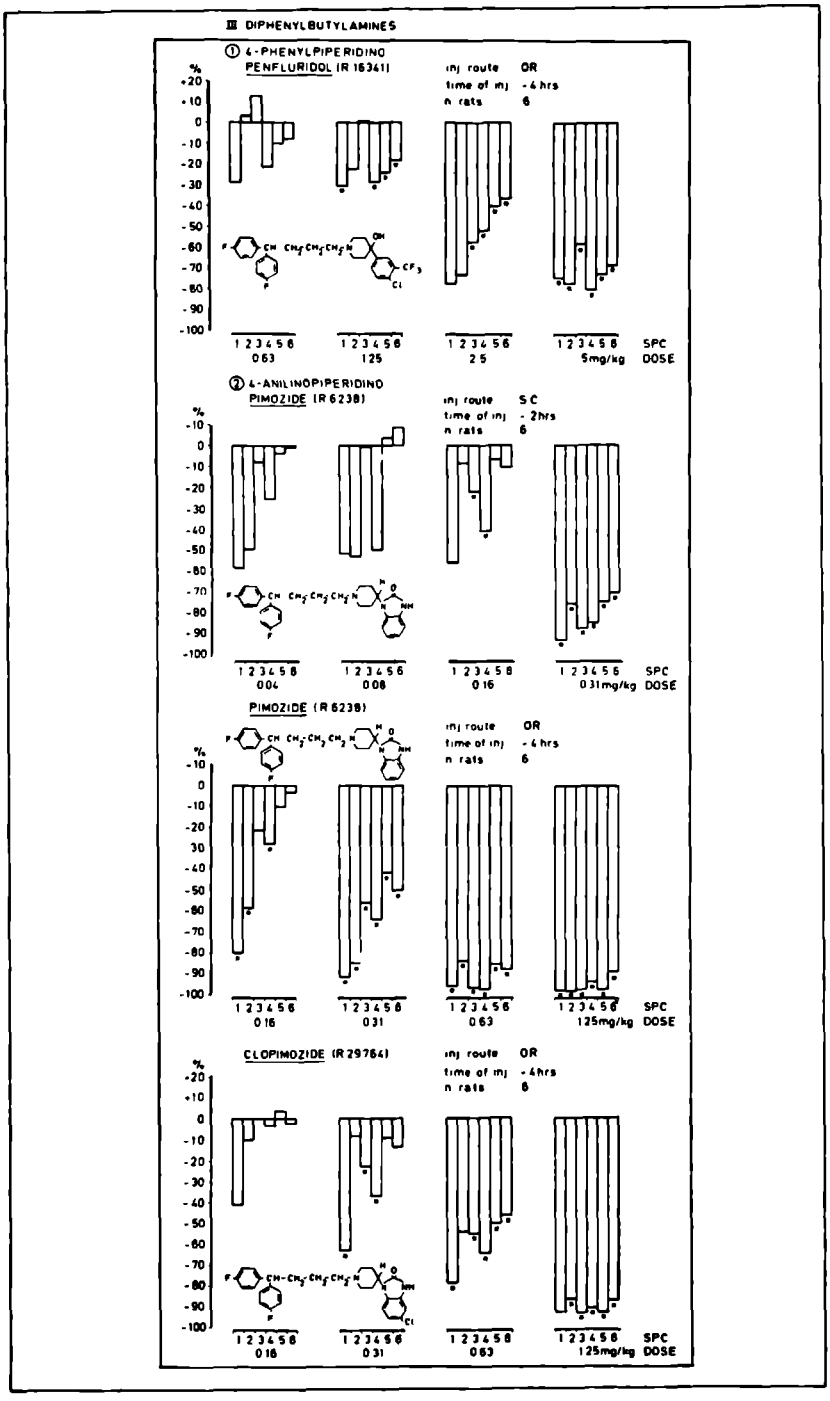


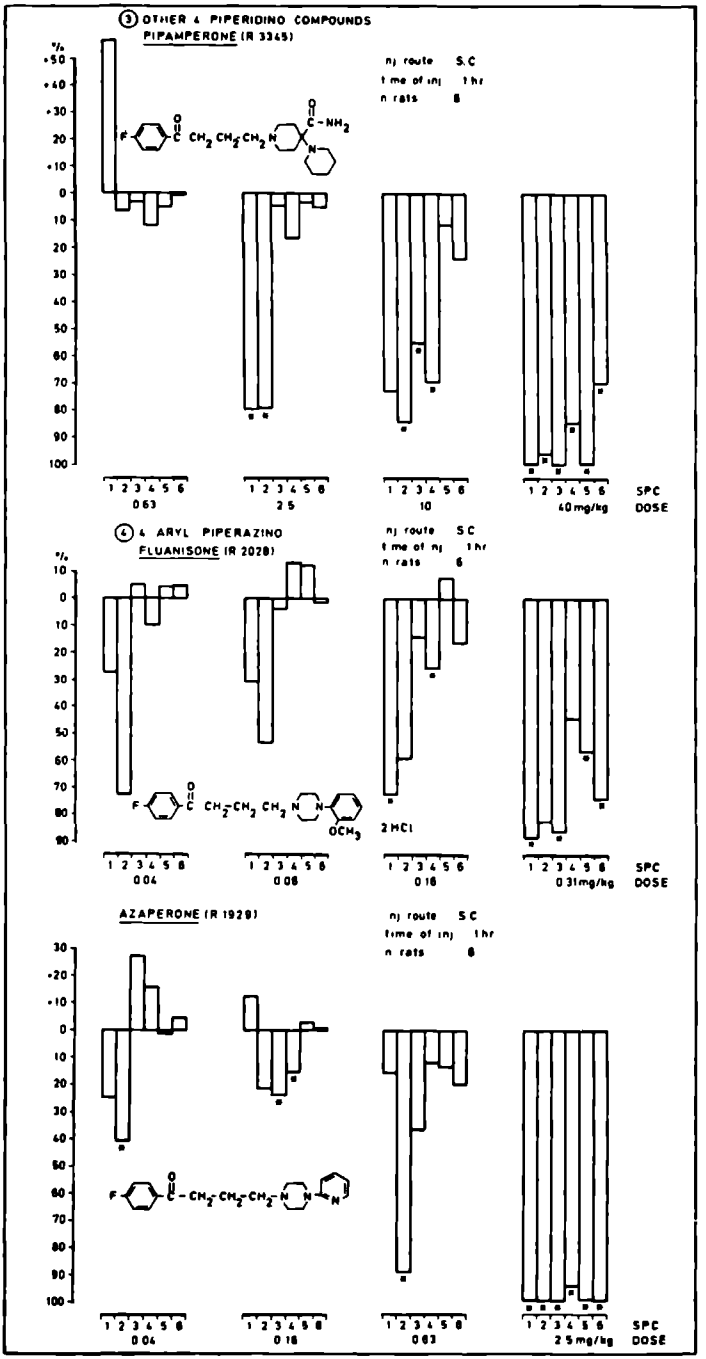
BROMPERIDOL (R 11333)

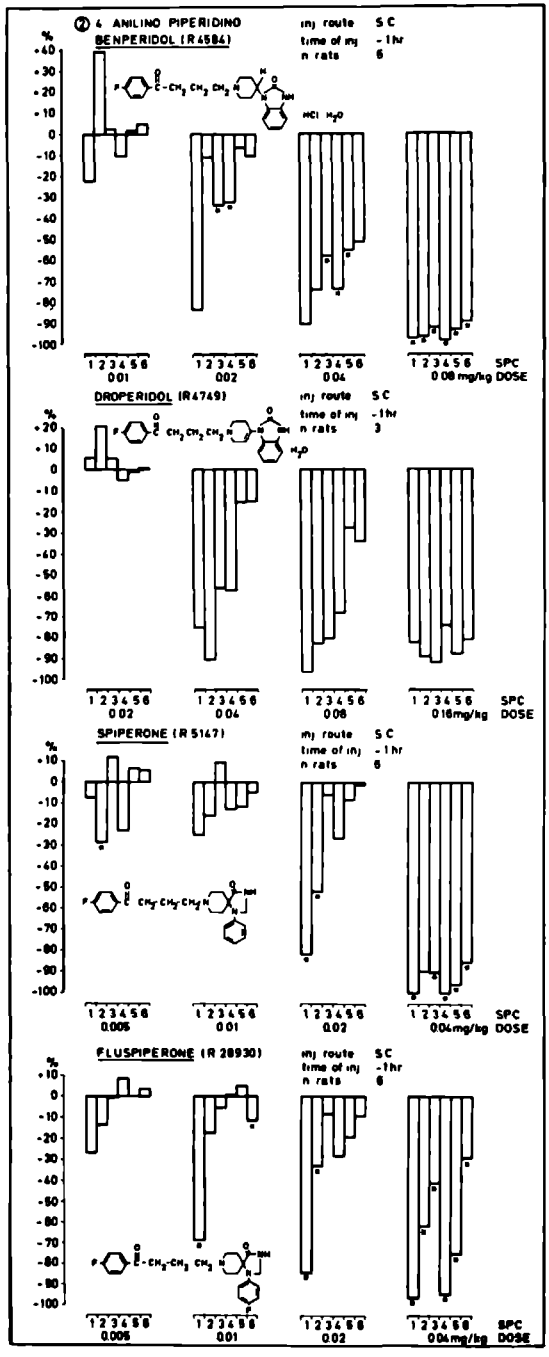


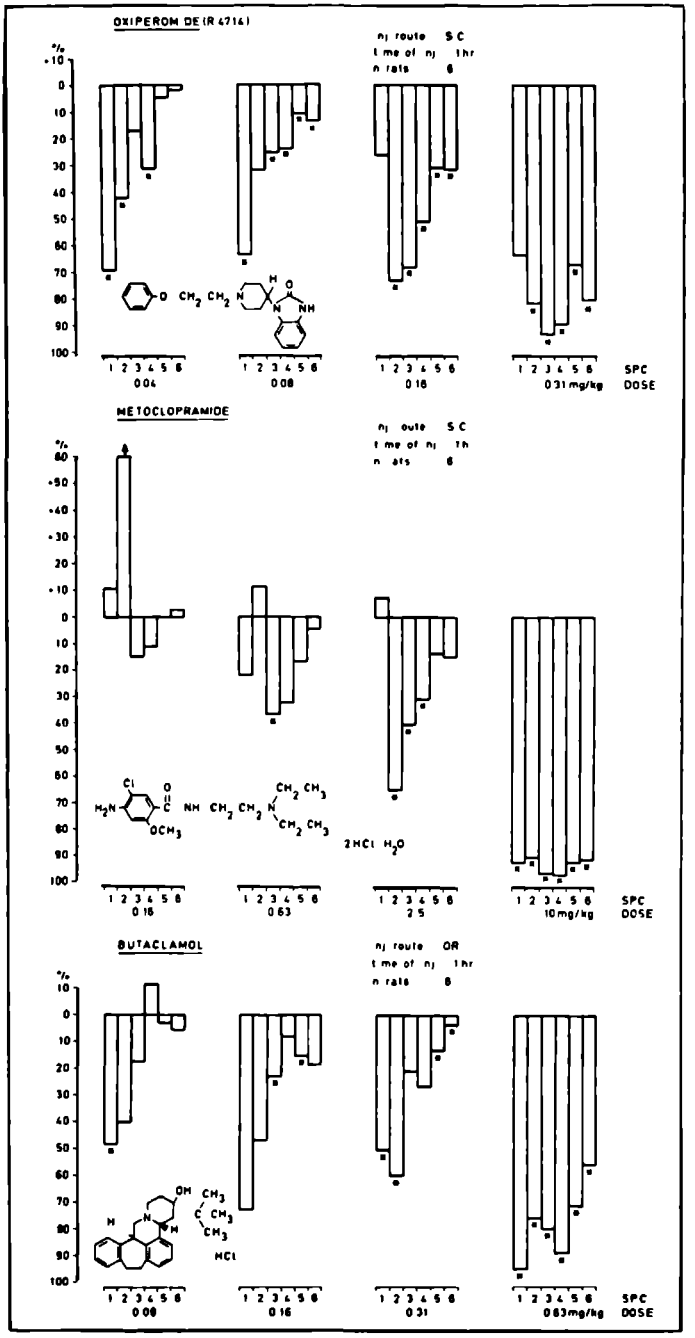
MOPERONE (R 1658)




III DIPHENYLBUTYLAMINES
① 4-PHENYLPIPERIDINO
PENFLURIDOL (R 16341)
inj route OR
time of inj - 4 hrs
n rats 6
1 2 3 4 5 6
0 63
1 2 3 4 5 6
1 25
1 2 3 4 5 6
2 5
1 2 3 4 5 6
5mg/kg
SPC DOSE
② 4-ANILINOPIPERIDINO
PIMOZIDE (R 6238)
inj route SC
time of inj - 2hrs
n rats 6
1 2 3 4 5 6
0 04
1 2 3 4 5 6
0 08
1 2 3 4 5 6
0 16
1 2 3 4 5 6
0 31mg/kg
SPC DOSE
PIMOZIDE (R 6238)
inj route OR
time of inj - 4 hrs
n rats 6
1 2 3 4 5 6
0 16
1 2 3 4 5 6
0 31
1 2 3 4 5 6
0 63
1 2 3 4 5 6
125mg/kg
SPC DOSE
CLOPIMOZIDE (R 29764)
inj route OR
time of inj - 4hrs
n rats 6
1 2 3 4 5 6
0 16
1 2 3 4 5 6
0 31
1 2 3 4 5 6
0 63
1 2 3 4 5 6
125mg/kg
SPC DOSE


③ OTHER 4 PIPERIDINO COMPOUNDS
PIPAMPERONE (R 3345)
inj route S.C
time of inj 1 hr
n rats 8
%
+50
+40
+30
20
+10
0
10
20
30
40
50
60
70
80
90
100
1 2 3 4 5 6
0.63
2.5
10
40 mg/kg
SPC
DOSE
④ 4 ARYL PIPERAZINO
FLUANISONE (R 2028)
inj route S.C
time of inj 1 hr
n rats 6
%
10
0
10
20
30
40
50
60
70
80
90
2 HCl
1 2 3 4 5 6
0.04
0.08
0.16
0.31 mg/kg
SPC
DOSE
AZAPERONE (R 1929)
inj route S.C
time of inj 1 hr
n rats 8
30
+20
+10
0
10
20
30
40
50
60
70
80
90
100
1 2 3 4 5 6
0.04
0.16
0.63
2.5 mg/kg
SPC
DOSE


② 4 ANILINO PIPERIDINO
BENPERIDOL (R4584)
inj route S C
time of inj - 1 hr
n rats 6
HCl H2O
1 2 3 4 5 6
0.01
0.02
0.04
0.08 mg/kg
SPC
DOSE
DROPERIDOL (R4749)
inj route S C
time of inj - 1 hr
n rats 3
H2O
0.02
0.04
0.08
0.16mg/kg
SPIPERONE (R 5147)
inj route S C
time of inj - 1 hr
n rats 6
0.005
0.01
0.02
0.04mg/kg
FLUSPIPERONE (R 28930)
inj route S C
time of inj - 1 hr
n rats 6
0.005
0.01
0.02
0.04mg/kg


OXIPEROM DE (R 4716)
inj route S.C
time of inj 1 hr
n rats 6
%
+10
0
10
20
30
40
50
60
70
80
90
100
1 2 3 4 5 6
0.04
0.08
0.16
0.31 mg/kg
SPC DOSE
METOCLOPRAMIDE
inj route S.C
time of inj 1h
n rats 6
+50
+40
+30
20
+10
0.16
0.63
2.5
10 mg/kg
2HCl H2O
BUTACLAMOL
inj route OR
time of inj 1 hr
n rats 6
0.08
0.16
0.31
0.63 mg/kg
HCl

3.2.3. Potency

Although there are great differences between the neuroleptics with respect to chemical structure, biochemical and behavioural as well as clinical effects, they all decrease self-stimulation in a dose-dependent way. There are, however, considerable differences with respect to potency. In order to estimate quantitative differences between neuroleptics, ED_{50} values with confidence limits and potency ratios were calculated, as described in the following paragraphs.

The median effective dose, often referred to as ED_{50}, is a term used to characterize the potency of a treatment by reference to the amount (dose of a drug) which produces a response in 50 % of the cases. In practice: after defining a criterion (for our data: $\leqslant$ 79 %, which corresponds to the .05 probability level of distribution of the control values), one obtains data of the all-or-none type. Therefore it is possible to solve a dose-percent curve, by which doses are converted to logarithms and percent effect to probits (Logarithmic-probability paper enables one to plot the data in original units, but leaves one with the problem of converting log-probit equations to their arithmic equivalent). After the data have been plotted, a straight line is fitted through these points (for instance percentage lever-pressing rate as compared with control versus doses of the neuroleptic). A goodness-of-fit test is applied by performing a chi-square test (expected against observed values). If the test is acceptable, the ED_{50} value can be read off directly on the intersection of the plotted line and the 50 % line on the ordinate.

The confidence limits represent the values in between which the ED_{50} is supposed to lie. The width of these limits is influenced by the heterogeneity of the data besides the slope of the curves. If this heterogeneity proves to be significant, a correction for significant heterogeneous data is performed.

Additional tests can be carried out if it proves necessary to compare two or more drugs, i.e. a test for parallelism (slopes) and the estimate of the relative potency. If no significant deviation of parallelism can be found, tests to detect significant differences in potency can be carried out and potency ratios with confidence limits may be calculated.

For a detailed description of the procedures just described, see Litchfield and Wilcoxon (1949). The results of the tests are given in Table 1.

This Table gives the ED_{50} values of the neuroleptics, slopes, slope function, potencies and potency ratios of the neuroleptics as compared with those of the most potent compound, fluspiperone. The ED_{50} of pimozide (orally given) could not be calculated, since 3 out of 6 rats were already found positive at the lowest dose tested. Comparison with fluspiperone was made since no significant differences of parallelism was found with the most potent neuroleptic. As seen, thioridazine, the weakest neuroleptic is 659 times less potent than fluspiperone. The inhibition obtained with fluspiperone, spiperone, benperidol, bromperidol, haloperidol and droperidol does not differ significantly from one substance to another.

Table 1: ED_{50}-values with confidence limits, slopes, slope ratios and potency ratios obtained with 20 neuroleptics tested on brain self-stimulation. For details see text.

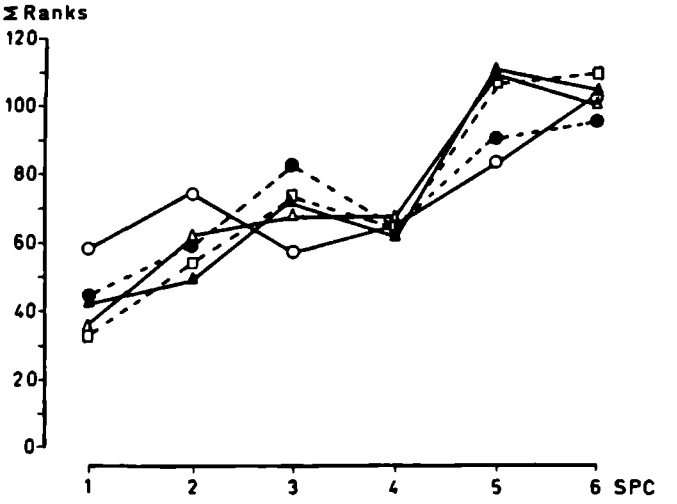
Compound	ED_{50} (limits)	Slope	Slope ratio (limits)	Potency ratio (limits)
Fluspiperone	0.0182 (0.0111-0.0299)	1.859	1.	1.
Spiperone	0.0185 (0.0106-0.0323)	2.008	1.08 (0.53-2.20)	1.02 (0.48-2.14)
Benperidol	0.0200 (0.0148-0.0270)	1.305	1.42 (0.90-2.25)	1.10 (0.62-1.96)
Bromperidol	0.0200 (0.0124-0.0322)	2.075	1.12 (0.57-2.17)	1.10 (0.55-2.19)
Haloperidol	0.0218 (0.0125-0.0380)	1.635	1.14 (0.63-2.05)	1.20 (0.57-2.52)
Droperidol	0.0285 (0.0193-0.0422)	1.414	1.31 (0.82-2.11)	1.57 (0.83-2.95)
Moperone	0.0330 (0.0238-0.0457)	1.334	1.39 (0.88-2.21)	1.81 (1.00-3.28) *
Oxiperomide	0.0569 (0.0374-0.0867)	1.692	1.10 (0.64-1.90)	3.13 (1.63-5.99) *
Clothiapine	0.0970 (0.066-0.143)	1.405	1.32 (0.82-2.14)	5.33 (2.84-9.99) *
Fluanisone	0.133 (0.073-0.243)	2.523	1.36 (0.54-3.42)	7.31 (3.34-16.0) *
Pimozide o.r.	0.160 (—)	—	—	—
Pimozide s.c.	0.160 (0.101-0.253)	2.013	1.08 (0.57-2.05)	8.79 (4.48-17.3) *
Butaclamol	0.270 (0.144-0.505)	2.188	1.18 (0.51-2.71)	14.8 (6.67-33.0) *
Clopimozide	0.340 (0.207-0.560)	1.865	1.00 (0.53-1.88)	18.7 (9.25-37.7) *
Chlorpromazine	0.513 (0.340-0.774)	1.673	1.11 (0.65-1.90)	28.2 (14.8-53.7) *
Metoclopramide	0.520 (0.180-1.50)	5.057	2.72 (0.73-10.1)	28.6 (8.88-92.0) *
Azaperone	0.534 (0.193-1.48)	2.460	1.32 (0.60-2.93)	29.3 (9.45-91.1) *
Penfluridol	1.36 (0.806-2.30)	1.924	1.03 (0.53-2.00)	74.7 (36.3-154) *
Pipamperone	6.35 (2.85-14.1)	2.719	1.46 (0.71-3.02)	349. (136 -894) *
Clozapine	7.84 (2.32-26.5)	4.590	2.47 (0.61-10.0)	431. (116-1606) *
Thioridazine	12.0 (4.17-34.5)	2.544	1.37 (0.59-3.15)	659. (205-2118) *

* Significantly different from fluspiperone ($p < .05$).

3.2.4. Control base-line

It appears from Fig. 1a-f, that there is an inverse relationship between base-line responding (response rates increase from SPC 1 to SPC 6) and neuroleptic-induced inhibition. That is: response inhibition is more pronounced at the low SPC's than at the high SPC's. This relationship was statistically substantiated by the Friedman two-way analysis of variance (see detailed description in Siegel, 1956, pp. 166-172). (Fig. 2). Basically, the test applied used the rank-order of the percentages inhibition obtained at the 6 SPC's with the 4 doses of the 20 neuroleptics. The analysis was made as follows: the percentage inhibition obtained with the 1st dose of a neuroleptic, at SPC 1, SPC 2 ... SPC 6, is given a rank-order (column); this is repeated for each of the 20 neuroleptics tested (rows).

Fig. 2: Friedman two-way analysis of variance carried out on the rank-orders of the percentages of inhibition obtained with 4 doses of 20 neuroleptics at the 6 SPC's (see details in text).



Friedman two-way analysis of variance

	Σ ranks							
	SPC 1	2	3	4	5	6	χ^2	P
1st Dose ●	44	60	83 5	66	91	96 5	27 81	<0 001
2nd Dose △	36	61	68	67	108	101	48 73	<0 001
3th Dose ▲	43	49	72	62	111	104	54 44	<0 001
4th Dose ○	58	74 5	57 5	64 5	83 5	103	21 07	<0 001
Overall effects □	32	54	73	65	107	110	62 99	<0 001

for example:

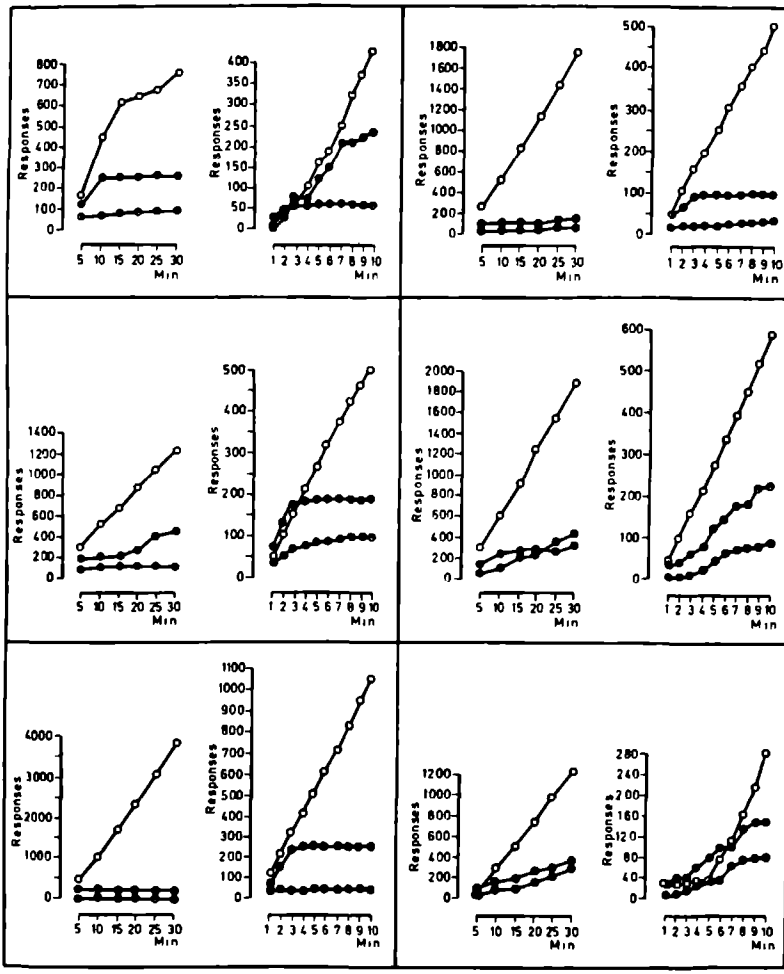
3rd dose	SPC 1	SPC 2	SPC 3	SPC 4	SPC 5	SPC 6
fluspiperone (% inhibition):	-84.7	-33.2	- 8.5	-28.3	-19.5	- 9.4
(rank-order):	1	2	6	3	4	5
spiperone (% inhibition):	-81.6	-51.9	- 5.9	-26.5	- 8.1	- 1.1
(rank-order):	1	2	5	3	4	6
...						
thioridazine (% inhibition):	-50.5	-18.8	-27.9	-48.2	- 9.6	-15.9
(rank-order):	1	4	3	2	6	5

Then, the sum of ranks is made and finally, $\chi_r 2$ is calculated according to the formula described by Siegel (1956, p. 168). The same is repeated for the 2nd, 3rd and 4th dose and for the sum of all doses.
If there is no preference for one of the conditions (SPC-effect), then one finds a nearly equal sum of ranks; if not, one can expect a systematic effect. It was found that with each of the doses tested, there is a systematic relationship between SPC and percentage inhibition, i.e. high inhibition (low sum of ranks) for low SPC's and vice versa ($p < .002$).

3.2.5. Discussion

All neuroleptics tested induced a dose-related inhibition of self-stimulation. The dose-response curves are quite similar, but the neuroleptics differ largely with respect to potency. However, as described in section 6, neuroleptics differ largely with respect to their effects on DA and NA.
Although self-stimulation is nearly completely suppressed by the highest dose of the neuroleptics tested, rats tend to self-stimulate at normal or higher rates than control animals during the first minutes of the session. Fig. 3 illustrates such an observation (similar observations were mentioned by Liebman and Butcher, 1974; Rolls et al., 1974b). This was recently confirmed by Fouriezos and Wise (1976) and discussed as follows. The temporal pattern of responding suggests that cessation of responding occurs in a similar way to extinction. If neuroleptics block the motor system, one would not expect the rats to start self-stimulating.
The latter observation not only suggests that the ability to press a lever is intact, but also that the anticipation of brain-stimulation reward may be unaffected. The cues associated with self-stimulation (conditioned motivation, i.e. smell, sight of the lever, etc.) are still present and induce the rats to start lever-pressing. The lack of sustained responding is not related to drug-onset, because lever-pressing occurs whenever the rats are put in the self-stimulation cage after drug-injection (Fouriezos and

Fig. 3: Self-stimulation response rates of 6 rats obtained after the s.c. injection of saline (o—o) or haloperidol (0.08 mg/kg) (●—●) and during extinction (⊙—⊙) (no brain-stimulation available).



Wise, 1976). This observation rather suggests that the reinforcing value of brain-stimulation is lowered or eliminated after high doses, just as it is in extinction.

A mechanism which could account for a lowering of the reinforcing value of the brain-stimulation is a drug-induced increase of the threshold for brain-stimulation. The latter was originally shown with chlorpromazine by Stein (1962b). This is exactly the opposite of the effects obtained with CNS-stimulants (see previous chapter, section 3.2). Experiments along these lines, however, have not been carried out using other neuroleptics. Response inhibition was more pronounced at the low SPC's than at the high ones. Similar observations, using a different method, were described for pimozide by Liebman and Butcher (1973). These authors showed that pimozide (0.35 and 0.5 mg/kg, given i.p., 3 hrs before the test) reduced self-stimulation for current intensities yielding 50 to 75 % of maximal rate. When the current was doubled, lever-pressing increased to base-line level. These findings are difficult to explain in terms of a performance effect, because one would expect an inhibition of the response rates, regardless of the particular SPC used. The differential inhibition suggests that the neuroleptic inhibitory property depends on the motivational strength of the stimulation.

Within a given structure, different response rates are obtained by varying the SPC's and possibly reflect a different rewarding value.

One could state that behaviour operating at a low motivational level is more susceptible to the neuroleptic-induced inhibition than behaviour maintained at a high motivational level. A low intensity or a low frequency stimulation is less reinforcing. Rats do not work continuously to obtain the reward, and the response rates are often erratic. Consequently, the expectancy is low and the habit strength less, than when rats work for higher intensities or frequencies of stimulation. In the latter case, the expectancy of reward is stronger.

Neuroleptics do not interfere with self-stimulation by altering the general activity level, or by disturbing the motor function, but maybe by lowering the reinforcing value. Whether neuroleptics also affect reward is still an open question.

Valenstein and Meyers (1974) developed a «rate-free» test of self-stimulation, which does not require lever-pressing. In short, the apparatus used is a shuttle box with a tilt platform. Moving the animal to one part of the cage closes a microswitch which activates programming equipment, so that the rat automatically obtains brain-stimulation. The time spent in the «active part» of the cage gives an indication of «self-stimulation». The programming is such that the rat has to move only a few times during an experimental session.

In the rate-free situation used by Liebman and Butcher (1974) they also measured gross locomotor activity. An increase in motor activity does not necessarily increase the time of stimulation. The authors showed, conversely, that a decrease in activity does not necessarily result in a reduction of brain-stimulation. Apomorphine, for instance, increased self-stimulation, despite a decreased locomotor activity. Liebman and Butcher (1974) showed that pimozide (0.35 mg/kg and 0.5 mg/kg)

reduced self-stimulation as measured in this rate-free situation, with rats bearing electrodes in the substantia nigra and lateral hypothalamus. In the rate-free situation, rats have only to walk to a part of the cage and, therefore, the obtained inhibition cannot be due to motor deficits. Because this rate-free test probably constitutes a more valid measure of the rewarding value of the stimulation, the authors concluded that pimozide reduced self-stimulation by interfering with the reward.
Although the experiments reported strongly support the consideration already stated above, that performance deficits are not a sufficient explanation of neuroleptic-induced inhibition, it is hard to accept that reward deficits account for the effects. Neuroleptics do not only inhibit positively motivated behaviour but negatively motivated behaviour as well. Doses almost identical to those inhibiting self-stimulation also inhibit Sidman shock-avoidance (see Table 2).
An important consideration, however, is that the sensitivity to the inhibitory effects of the neuroleptics might depend on the operant itself. This will be dealt with in an experiment reported in the next section.

4. LICK-EXPERIMENT

The inhibition obtained with neuroleptics is clearly base-line-dependent (see previous section). Some experiments (see for instance Huston and Ornstein, 1976) showed that brain-stimulation persisted after lesioning the nigral system, but rats were unable to perform complex responses, requiring orientation in space, such as lever-pressing. By analogy, the neuroleptic-induced inhibition might depend on the operant used. We therefore compared, in these experiments, the effectiveness of 4 selected neuroleptics on brain-stimulation obtained after either pressing a lever or licking a steel ball.

4.1. Methods

Rats were trained to receive brain-stimulation either by licking a stainless steel ball or by pressing a lever, during the same session. Since the licking rate is very rapid, a fixed ratio reinforcement schedule 3:1 (FR 3) was applied during the licking period. Lever-pressing was carried out on a continuous reinforcement schedule (CRF). Half of the rats were required to lick for brain-stimulation for 15 min, followed by 15 min of lever-pressing (Group 1). Other rats were given the opposite sequence (Group 2). For each rat, the sequence remained the same during the whole experiment. The stimulation parameters of brain-stimulation were the same for licking as well as for lever-pressing (SPC 6).
Rats were run in daily half hour sessions, 5 days a week. Stable performance (variation within 10 % of the mean over 3 days) for both licking and lever-pressing, was reached within 3 weeks.
Groups of 6 rats were treated with 4 doses of a neuroleptic: pimozide, haloperidol, pipamperone or azaperone (Table 2, Fig. 4). Pimozide was injected s.c., 2 hrs before the session, while the other neuroleptics were given s.c., 1 hr before the session. There was an interval of at least 2 sessions between each drug-treatment.

Fig. 4: Percentage response rates as compared with control for lever-pressing (o — o) and licking (● — ●) for brain-stimulation after 4 doses of the neuroleptics indicated. Group 1 started the self-stimulation session with licking (15 min), group 2 started the session with lever-pressing (15 min).

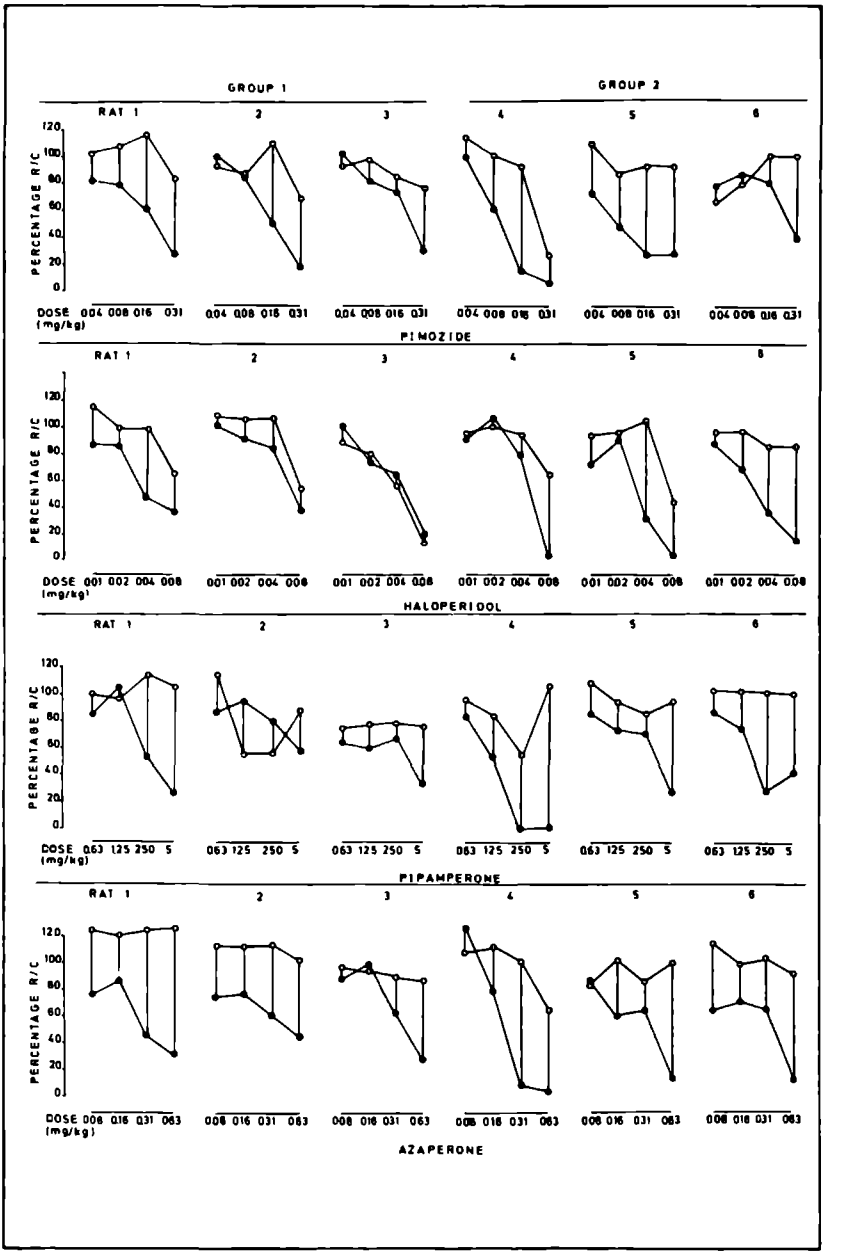


Table 2: *Total number of licks and lever-pressings for brain stimulation obtained after saline or drug-injection, with 3 rats which licked for 15 min followed by 15 min of lever-pressing (group 1), and with 3 rats which pressed a lever for 15 min, and than licked for 15 min (group 2).*

Drug	Dose (mg/kg)	Group 1		Group 2		Licking		Lever-pressing	
		Licks	Lever-press.	Licks	Lever-press.	Total	% drug / saline	Total	% drug / saline
PIMOZIDE	saline	4035	2878	6292	2191	10327		5069	
	0.04	3966	2818	5545	2130	9511	92.1	4948	97.6
	saline	4370	2845	6749	2542	11119		5387	
	0.08	3608	2756	4546	2306	8154	73.3	5062	93.9
	saline	5023	2268	6085	2131	11108		4399	
	0.16	3188	2662	2189	2041	5377	48.4 *	4703	106.9
	saline	5170	2595	5483	2147	10653		4742	
	0.31	1352	1971	1146	1509	2498	23.4 *	3480	73.3 *
HALOPERIDOL	saline	3139	1856	6296	2217	9435		4073	
	0.01	3033	1962	5530	2142	8563	90.8	4104	100.7
	saline	3111	2098	5153	2191	8264		4289	
	0.02	2748	2040	4832	2177	7580	91.7	4217	98.3
	saline	3207	2280	6132	2107	8301		4387	
	0.04	2242	2082	3154	2009	5396	65.0 *	4091	93.2
	saline	2896	2213	5094	1989	7990		4202	
	0.08	1043	1060	364	1323	1407	17.6 *	2403	57.2 *
PIPAMPERONE	saline	4487	2075	7306	1999	11793		4074	
	0.63	3520	1999	3958	2040	7478	63.4	4039	99.1
	saline	4389	2290	6051	2030	10440		4320	
	1.25	3822	1678	3831	1888	7653	73.3	3566	82.5
	saline	4866	2354	4805	2214	9671		4568	
	2.50	3391	1820	1331	1750	4722	48.8 *	3570	78.1
	saline	4410	2635	4217	2008	8627		4643	
	5.00	1901	2326	697	2046	2598	30.1 *	4372	94.1
AZAPERONE	saline	5142	2501	5464	2256	10606		4757	
	0.08	4141	2708	5261	2346	9402	88.6	5054	106.2
	saline	4687	2627	6313	2201	11000		4828	
	0.16	4260	2847	4514	2303	8774	79.7	5150	106.6
	saline	4811	2563	5443	2091	10254		4645	
	0.31	2818	2681	2721	2050	5539	54.01*	4731	101.8
	saline	5071	2530	5433	2162	10504		4692	
	0.63	1792	2609	709	1883	2501	23.8 *	4492	95.7

* $p < .05$.

The Wilcoxon matched-pairs signed-ranks test (one-tailed probability, $p < .05$) was used as a test for significance of differences between drug- and control-session.

4.2. Results

Table 2 depicts the total number of licks and lever-pressings during saline- and drug-session. Fig. 4 depicts the percentage response rates obtained after drug-treatment as compared with the median of the pre-drug control response rates for each individual rat.

Saline-treated rats: the licking response rates always exceeded the lever-pressing response rates in total, and for each individual rat, except for rat 3 during the haloperidol experiment. The licking-rate was higher in group 2 (which started the session with lever-pressing) than in group 1. The lever-pressing rate, on the other hand, was higher in group 1 than in group 2 (Table 2). The total number of licks was two times and two to three times the number of lever-pressings in group 1 and group 2 respectively.

Drug-treated rats: in general, a dose-related inhibition of licking for brain-stimulation was found, while the inhibition of lever-pressing was only marked at the highest dose of the neuroleptics tested (Table 2), except for rat 3 in the haloperidol-experiment. The rats of group 2, which scored the highest number of licks, were more sensitive to the neuroleptic-induced inhibition than the rats of group 1 (Table 2).

The estimated ED_{50}-values of inhibition were:

		Group 1	Group 2
for pimozide	licking	0.19	0.13
	lever-pressing	> 0.31	> 0.31
for haloperidol	licking	0.053	0.039
	lever-pressing	> 0.08	> 0.08
for pipamperone	licking	3.86	1.92
	lever-pressing	> 5	> 5
for azaperone	licking	0.42	0.27
	lever-pressing	> 0.63	> 0.63

In conclusion: the lick-response is more inhibited than lever-pressing; the group (2) which scored the highest number of licks was more sensitive to drug-effects; within the respective dose-range tested, all neuroleptics elicit similar effects.

4.3. Discussion

In the context of the rat's development, licking has been associated with different functions, such as licking at a tube to obtain water, licking as a cleaning habit and so on. Lever-pressing on the other hand, is a learned

response and is not part of the rat's natural repertoire but appears only in one situation, namely as a means of obtaining brain-stimulation. One could argue that the consummatory response must be more susceptible to the neuroleptic effects than a response lacking. However, Rolls et al. (1974b) showed that spiroperidol attenuated water-licking from a tube less than lever-pressing for self-stimulation.
It was stated in 3.2.4. that high response rates were less susceptible to the inhibitory effects of neuroleptics. This was confirmed for lever-pressing in this experiment. However, the licking rate was higher than the lever-pressing rate and yet was more sensitive to the inhibition. Further, the rats scoring the highest number of lick-responses (group 2) were inhibited at lower doses than the group (1) which scored fewer licks. Moreover, the 4 neuroleptics elicited rather similar effects, although they caused different behavioural effects at high dose levels: haloperidol and pimozide causing catalepsy and pipamperone and azaperone causing sedation (see also section 6).
The differential inhibition of licking and lever-pressing could be partially due to the schedule applied during the licking period (FR-3) and lever-pressing period (CRF). Licking was more sensitive than lever-pressing in both groups, although group 1 licked far less than group 2; the numbers of stimulations received by group 2 for lever-pressing and for licking were almost equal. The differential sensitivity cannot, therefore, be sufficiently explained by the schedule differences.
Apparently, another factor is responsible for the differential sensitivity to the inhibitory effect. Neuroleptics might for instance differentially affect the motor system involved in the reflexive lick-response and the motor system involved in lever-pressing. This remains speculative since there are no experiments dealing with differential influence on different motor systems.
In conclusion: it appears that the neuroleptic-induced inhibition of self-stimulation depends on the operant used. However, it remains difficult to present a conclusive interpretation of the differential sensitivity. On the basis of the present experiments, it cannot be stated affirmatively whether the differential inhibition is a performance - or reinforcement - effect.

5. IMPLANTATION SITE AND SPECIES DIFFERENCES

5.1. Implantation site

One of the structures which has been extensively explored in self-stimulation is the lateral hypothalamic area. Our studies also deal with self-stimulation in the lateral hypothalamus. Obviously, one could ask whether the inhibitory properties of neuroleptics are related to, or rather independent of, the implantation site.
Pimozide is a specific dopaminergic blocking agent (Andén et al., 1970). One would expect pimozide to reduce only partially or to fail to inhibit self-stimulation elicited in purely noradrenergic cell bodies such as the locus coeruleus, origin of the dorsal noradrenergic bundle. The under-

lying assumption is that pimozide selectively disrupts a DA-mediated system.
The experiments of Ritter and Stein (1973) apparently confirmed this hypothesis: 1 mg/kg of pimozide injected s.c. as an aqueous suspension, inhibited self-stimulation in the locus coeruleus (89.7 % of control) less than in the medial forebrain bundle (69.8 % of control).
Liebman and Butcher (1974) also showed that 0.5 mg/kg of pimozide inhibited self-stimulation in the substantia nigra slightly more effectively than in the lateral hypothalamus.
Site-dependent effects have been described for other neuroleptics.
Rolls et al. (1974a) described a dose-related inhibition of self-stimulation by spiroperidol, in the nucleus accumbens, the septal region, the hippocampus, the anterior hypothalamus, the lateral hypothalamus and the ventral tegmental area. The inhibition was relative to base-line, but some regional differences were apparent. For example, the response rates obtained after 0.05 mg/kg of spiroperidol as compared to control, were approximately 40 %, 20 %, 0 %, 60 %, 50 % and 70 % for the respective structures just mentioned.
Stark et al. (1969) described that chlorpromazine inhibited self-stimulation in the septum, anterior and posterior hypothalamus and in the ventral tegmentum. The posterior hypothalamic self-stimulation was somewhat more affected by the lowest dose of chlorpromazine.
Olds and Travis (1959) and Olds et al. (1957) described anatomical differences with respect to the inhibitory effects of chlorpromazine. They noted that chlorpromazine strongly inhibited self-stimulation in the ventral posterior hypothalamus, was less effective in the septal region and had a negligible effect in the anterior hypothalamic area.
In contrast, Phillips et al. (1975) obtained a similar dose-related response inhibition with pimozide and haloperidol in rats self-stimulating in the dorsal noradrenergic bundle and in the dopaminergic nucleus accumbens. Similarly, Liebman and Butcher (1973) found no difference between the effects of pimozide injected in rats self-stimulating in the lateral hypothalamus or in the mesencephalic central gray area. Moreover, the latter structure does not contain dopaminergic neurons (Ungerstedt, 1971a).
Definitive conclusions cannot be derived from the reported experiments. Apparently, methodological problems are involved. Without being exhaustive, it is suggested that the following factors could be responsible for these discrepancies: the differential site-dependent effects found by some authors, might reflect the central distribution of the drug over a period of time; state-dependent effects might play a rôle and, more generally, the doses used, the injection route, etc. In the next section, species-related and site-dependent-related self-stimulation are described.

5.2. Species

5.2.1. Introduction

For obvious reasons, rats were the subjects of choice for the pharma-

cological self-stimulation experiments. Drug-results obtained in one species may not be generalized to other species without restrictions. A good example of species-related effects is the acute effects of narcotic analgesics. Morphine, or related drugs cause catatonia in rats (rigidity and loss of righting reflex), excitation in mice and sham-rage in cats.
There are only two reports of drug-effects on self-stimulation in other species. Stark (1964) tested cholinergics, anticholinergics, serotonin-like and serotonin-antagonistic drugs in dogs. Horovitz et al. (1962) studied the effects of chlorpromazine in cats. They described that chlorpromazine (2.5, 3.75 and 5.0 mg/kg) decreased self-stimulation in the lateral hypothalamus and equally in the caudate nucleus. In 2 out of 7 cats, 0.5 and 1.0 mg/kg of chlorpromazine did not affect responding.
The effects of different doses of pimozide, haloperidol and pipamperone on self-stimulation in dogs have been investigated (briefly reported in Wauquier, 1975). Dogs are extremely suitable for self-stimulation experiments because of their extensive behavioural repertoire. The aims of our studies were: to investigate whether neuroleptics inhibited self-stimulation in the same way as in rats, and whether neuroleptic-induced inhibition depended on the brain-structure.

5.2.2. Methods

Seven beagle dogs were implanted with bipolar stainless steel electrodes in the anterior part of the basal forebrain, i.e. the nucleus accumbens and the lateral preoptic region; in the basolateral amygdala, the lateral hypothalamus and the substantia nigra. At least 3 electrodes out of 6 implanted in each dog, sustained self-stimulation. Dogs were trained to lever-press for brain-stimulation during x times 10-min periods (x being the number of positive electrodes). After training for at least 6 sessions, the dogs were treated with pipamperone (0.16, 0.31, 0.63, 1.25 and 2.50 mg/kg) given s.c., 1 hr before the session; pimozide (0.04, 0.08, 0.16, 0.31 and 0.63 mg/kg), given s.c. 4 hrs before the session, and haloperidol (0.04, 0.08, 0.16, 0.31 and 0.63 mg/kg) given s.c., 2 hrs before the session. The time-intervals were selected on the basis of pilot experiments in which different doses of these neuroleptics had been given to labradors, and self-stimulation measured for 10-min periods, 1 hr, 2 hrs, 4 hrs and 6 hrs after injection.
The histology of electrode placements was determined as follows: brains were embedded in celloidin and cut on a microtome at 100 microns. The slices containing the electrode tip were selected and stained by Weil's method. Photographs were made and brain structures outlined on transparent paper. Examples of electrode placements sustaining self-stimulation are depicted in Fig. 5.

5.2.3. Results

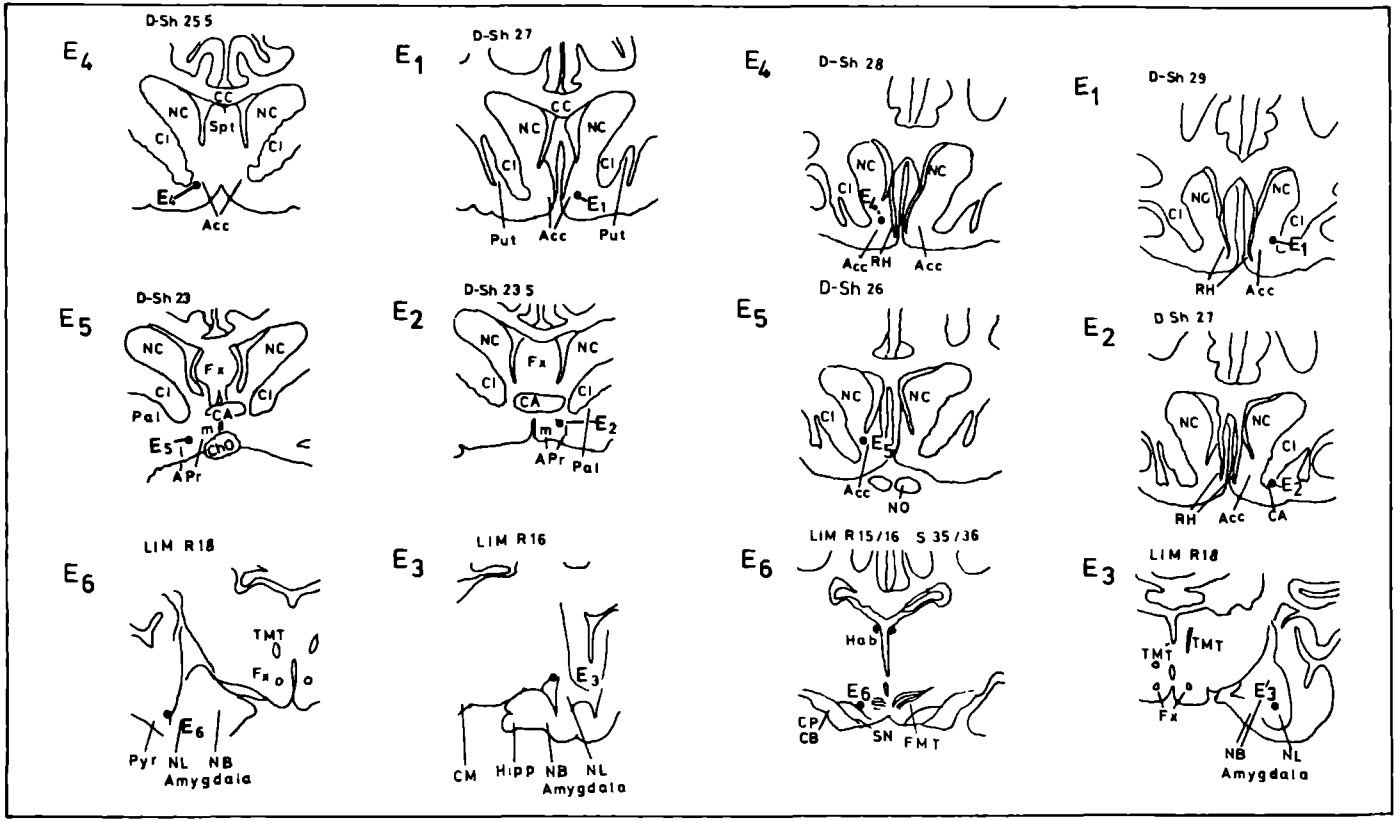
The results of the pilot experiments are depicted in Fig. 6. As can be seen, the highest inhibition is obtained 4 to 6 hrs after pimozide-injection, 2 to 4 hrs after the haloperidol-injection and 1 to 2 hrs after the pipamperone injection.

Fig. 5: *Electrode placements of 2 dogs. D-Sh and LIM refer to the anterior position according the atlas of Dua-Sharma et al. (1970) and Lim et al. (1960) respectively. Electrode E1, E2 and E3: right side of the brain; E4, E5 and E6: left side of the brain.*

Dog left:
position E1 and E4 in nucleus accumbens
E2 and E5 in lateral peoptic region
E3 and E6 virtually outside amygdala
(Self-stimulation in E1, E2, E4 and E5)

Dog right:
position E1 and E2 ventral to the caudate nucleus
and between internal capsula and nucleus accumbens
E4 and E5 in nucleus accumbens
E3 in basolateral amygdala
E6 in substantia nigra
(Self-stimulation in E1, E2, E3, E4 and E6)

Abbreviations:
NC - caudate nucleus, CC - corpus callosum, Spt - septum, CI - internal capsule, Acc - nucleus accumbens, Put - putamen, Fx - fornix, CA - anterior commissure, Pal - globus pallidus, APr - preoptic area, m - medial, l - lateral, ChO - optic chiasm, TMT - tractus mammillo-thalamicus, Pyr - lobus pyriformis, Hipp - hippocampus, CM - corpora mammillaria, amygdala: NL - lateral nucleus, NB - basal nucleus (nomenclature after Lim), RH - rudimentum hippocampi, NO - optic nerve, Hab - habenula, CP - cortico-pontine and CB - cortico-bulbar tracts, SN - substantia nigra, FMT - fasciculus mammillo-tegmentalis, SGC - substantia grisea centralis, Aq - aqueductus cerebri, $E_{1.....7}$ - tip of the electrode.


E4
D-Sh 25 5
CC
NC
Spt
NC
Cl
Cl
E4
Acc
E1
D-Sh 27
CC
NC
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D-Sh 28
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Cl
E4
Acc
RH
Acc
E1
D-Sh 29
NC
NC
Cl
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E1
RH
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E5
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E6
Pyr
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Amygdala
E3
LIM R16
E3
CM
Hipp
NB
NL
Amygdala
E6
LIM R15/16 S 35/36
Hab
E6
CP
CB
SN
FMT
E3
LIM R18
TMT
TMT
E3
Fx
NB
NL
Amygdala

Drug-effects were obtained on 31 electrodes of 7 dogs. Fig. 7 depicts the response rates in relation to control rates after neuroleptic treatment. The number of electrodes tested is indicated.
The three neuroleptics inhibited self-stimulation obtained in various brain-structures of the dog. As compared with the inhibition of self-stimulation in rats, there are three important differences: the potency ratios between the neuroleptics, site-dependent effects and the fact that pimozide- or haloperidol-induced inhibition is associated with apparent behavioural changes.
Firstly, pipamperone inhibits self-stimulation in dogs at doses 4 to 16 times lower than those required in rats; the opposite holds for haloperidol, while pimozide is rather similarly active in rats. Further, smooth linear dose-related inhibition was not found at all electrode-sites tested. Atypical response curves as seen with pimozide in the nucleus accumbens, the lateral preoptic and substantia nigra, and with haloperidol in the lateral hypothalamus are particularly due to the effects of these neuroleptics on individual dogs.
Secondly, different sensitivities to neuroleptic-induced inhibition, related to the brain-structure were apparent. With 0.31 mg/kg of pimozide, the numbers of lever-pressings as compared with that of the controls were 47.8 %, 41.2 %, 11.1 % and 51.3 %, for the nucleus accumbens, the lateral preoptic, the substantia nigra and the lateral hyothalamus respectively. With 0.63 mg/kg of haloperidol, lever-pressing was 58.8 %, 41.7 %, 21.2 % and 80.3 % as compared with control values for the nucleus accumbens, the lateral preoptic, the substantia nigra and lateral hypothalamus respectively. With 2.5 mg/kg of pipamperone, lever-pressing was 43.3 %, 56.4 % and 8.75 % as compared with control values, for the nucleus accumbens, the lateral preoptic and basolateral amygdala respectively.
Thirdly, behavioural changes accompanied the self-stimulation inhibition induced by pimozide and haloperidol. For instance, whilst neuroleptic-treated dogs exhibited some opposition to being walked to the experimental room, they walked back to their home cage without resistance. Further, the response pattern became irregular. Instead of an almost equal number of lever-pressings per minute, prolonged periods of non-pressing occurred, while at other moments the dogs pressed the lever at an extremely fast rate. This occurred in 2 dogs in particular and resulted in a total amount of lever-pressings nearly equal to control rates. The latter is the reason for non-linear dose-related inhibition. During the periods of non-pressing, dogs often stereotypically scratched the floor with both forepaws.

5.2.4. Conclusion

In conclusion: self-stimulation in dogs is apparently sensitive to the suppressive effects of preferentially noradrenergic blocking agents (see 6). At the doses used, pipamperone only interferes with NA receptors (at least in rats, see Andén et al., 1970). The question of whether noradrenergic-mediated neurotransmission plays a primary rôle in self-stimulation in dogs merits further investigation. However,

Fig. 6: Self-stimulation response rates of 3 dogs, as compared with control response rates, obtained in 10-min periods at different time-intervals (1, 2, 4 and 6 hrs) after the s.c. injection of 5 doses of pimozide, haloperidol and pipamperone. Electrode positioned in the lateral preoptic region.

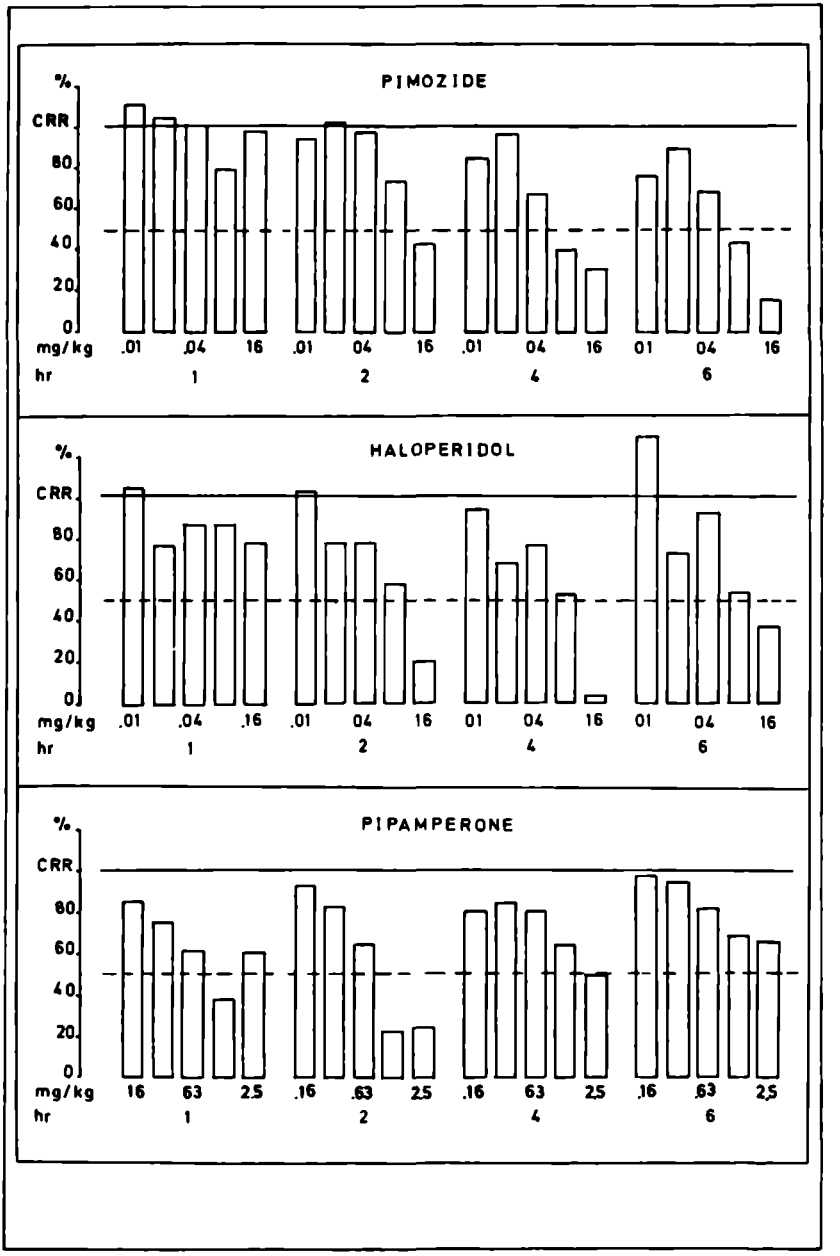
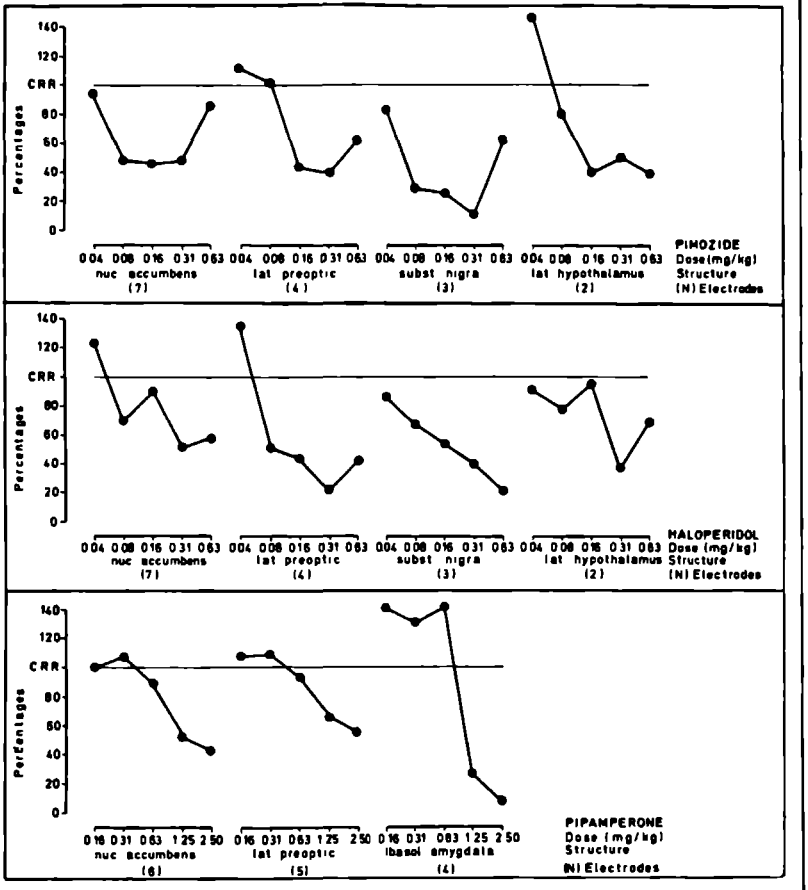


Fig. 7: Self-stimulation response rates in relation to control response rates (CRR = 100 %) after the injection of 5 doses of 3 neuroleptics, obtained with 7 dogs, self-stimulating in different brain structures (details see text).



pipamperone also inhibits self-stimulation of the DA-nucleus accumbens, which might support the concepts of Franklin et al. (1976) and Stephens et al. (1976), that DA self-stimulation also requires transsynaptic activation of NA-structures. The mutual dependence of both amines would explain many of the controversies about a specific rôle for either one of these amines. As described in some reports on neuroleptic-induced inhibition of self-stimulation in rats, the experiments with the dog also indicate that some brain sites are more sensitive than others. The pharmacokinetic distribution of drug may also explain the different sensitivities, because the order in which the electrodes were tested was different in the dogs. The results presented here again provide evidence that the neuroleptic-induced suppression is not in the first place a «response-effect».

6. SELF-STIMULATION AND PSYCHOTROPIC ASSAYS (1)

The previous section described the neuroleptic-induced inhibition on a quantitative basis. In spite of characteristics shared by all neuroleptics, these drugs are not a homogeneous group. The aim here is to describe the differentiation between the neuroleptics as based on different pharmacological tests. Further, appropriate methods make it possible to position the self-stimulation test with respect to other pharmacological experiments.

6.1. Classification of neuroleptics

Classifications of neuroleptics can be made on different bases such as chemical (e.g. Janssen, 1970, 1973), biochemical (e.g. Andén et al., 1970), pharmacological (e.g. Janssen et al., 1965a) and clinical (e.g. Bobon et al. 1972). Herein we describe classifications of neuroleptics as based on pharmacological and clinical activity.

6.1.1. Classification based on potency ratios

Qualitative observations and comparative pharmacology of a large group of neuroleptics have been described extensively over the past years (Janssen, 1970, 1972; Janssen and Van Bever, 1975; Janssen et al., 1965a, b, 1966, 1967; Niemegeers, 1974). These allowed the construction of neuroleptic activity spectra as based on potency and ratios between potencies.

Four main pharmacological tests (2) differentiate the neuroleptics: the induction of catalepsy (CA), palpebral ptosis (PP), the antagonism of amphetamine-induced stereotype behaviour (AM) and the antagonism of a lethal dose of norepinephrine (NE). The procedures used and criteria

(1) This section has been written in collaboration with P.J. Lewi.

(2) The serotonergic blocking effects as measured in the tryptamine-test will not be discussed here, but it should be mentioned that these tests add another dimension to the differentiation between neuroleptics.

applied to determine neuroleptic potency in these tests were described earlier (Niemegeers, 1974). The CA- and AM-test are indicative for predominant dopamine-blocking activity and the NE- and PP-test are indicative for a more pronounced noradrenergic blocking activity.
High doses of incisive neuroleptics cause catalepsy. Muscle tonus in the cataleptic rats is normal. The same neuroleptics antagonize stereotyped behaviour induced by amphetamine. These neuroleptics have antipsychotic activity and often cause extrapyramidal side-effects in the clinic.
High doses of sedative neuroleptics cause sedation and palpebral ptosis. These neuroleptics antagonize a lethal dose of norepinephrine. They have less, or are devoid of, antipsychotic activity.
The ED_{50}-values of the neuroleptics tested in self-stimulation, and in the CA-, PP-, AM- and NE-test are given in Table 3. The relative adrenolytic versus antipsychotic activity and the relative sedative versus neurologic

Table 3: *ED_{50}-values (mg/kg) after administration of various neuroleptics to brain self-stimulating (BS) rats, and after the following tests: amphetamine-antagonism (AM), norepinephrine-antagonism (NE), catalepsy (CA), palpebral ptosis (PP), Sidman-shock avoidance (SA), ambulation (AMB) and rearing (REA).*

	Compound	Tests							
	Generic name	BS	AM	NE	CA	PP	SA	AMB	REA
1	Azaperone	0.534	2.5	0.33	8.0	1.5	-	6.70	4.10
2	Benperidol	0.020	0.012	0.30	0 18	1.2	0.015	0.40	0.35
3	Bromperidol	0.020	0.053	7.24	0.12	1.7	0.045	-	-
4	* Butaclamol	0.270	0.31	>10	-	-	-	-	-
5	Chlorpromazine	0.513	0.60	0.60	2.3	2.3	1.2	4.5	3.7
6	* Clopimozide (1)	0.340	0.085	5.0	0.50	5.0	-	-	-
7	Clothiapine	0.097	0.20	0.89	-	-	0.2	-	-
8	* Clozapine	7 84	20	4.0	-	-	-	-	-
9	Droperidol	0.029	0.023	0.1	0.38	0.38	0.025	1.3	0.60
10	Fluanisone	0.133	0.20	0.1	2 0	0 65	0.12	2.0	0.70
11	Fluspiperone	0.018	0.020	-	-	-	-	-	-
12	Haloperidol	0.022	0.038	2.1	0.18	1.0	0 03	0.21	0,13
13	Metoclopramide	0.520	5.0	>160	19	32	-	-	-
14	Moperone	0.033	0 03	1.5	1.2	2.3	0.04	0.78	0.26
15	Oxiperomide	0.057	0.03	5	>40	2.5	-	-	-
16	* Penfluridol (1)	1.36	0.31	10	1.2	36	>0.63	-	-
17	* Pimozide	0.160	0.1	40	0.18	4.5	0.16	-	-
18	Pipamperone	6.35	2.5	3,0	16.5	2.7	5	25	15
19	Spiperone	0.019	0.02	1.2	0 036	0.27	0.015	0.11	0.055
20	Thioridazine	12.0	9.12	1 0	14	2.7	5	12	30

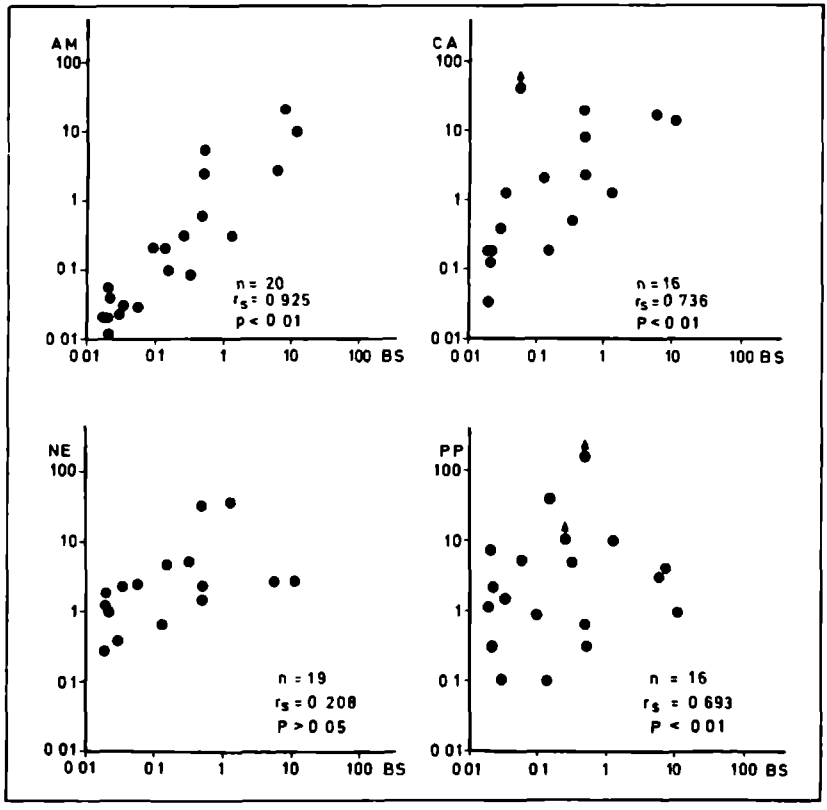
(1) The ED_{50}-values of the long-acting neuroleptics penfluridol and clopimozide were obtained 4 hrs after injection.

* Given orally.

effects, are indicated by the ratio of ED_{50}-based activities. A low ratio of NE/AM and PP/CA, is found with alpha-adrenolytic neuroleptics, which preferentially bloc the noradrenergic receptors that cause sedation in rats, and autonomic side-effects in human subjects. A high ratio NE/AM and PP/CA is found with incisive neuroleptics, which preferentially block the dopaminergic receptors, that induce catalepsy in rats and cause extrapyramidal side-effects in man. The separation between incisive and sedative neuroleptics is evidently not an all-or-none phenomenon, but a continuum.

The ED_{50}-values of the neuroleptics tested in self-stimulation were correlated with the ED_{50}-values obtained in the different tests mentioned (Janssen and Van Bever, 1975), i.e. CA, PP, NE and AM (Spearman rank-order correlation) (Fig. 8).

Fig. 8: Correlation (Spearman rank-order correlation r_S) between the ED_{50}-values of the inhibition on brain self-stimulation (BS) and the ED_{50}-values of antagonism of amphetamine-induced stereotypies (AM), catalepsy (CA), norepinephrine-antagonism (NE) and palpebral ptosis (PP), obtained with various neuroleptics (n) (see Table 2).

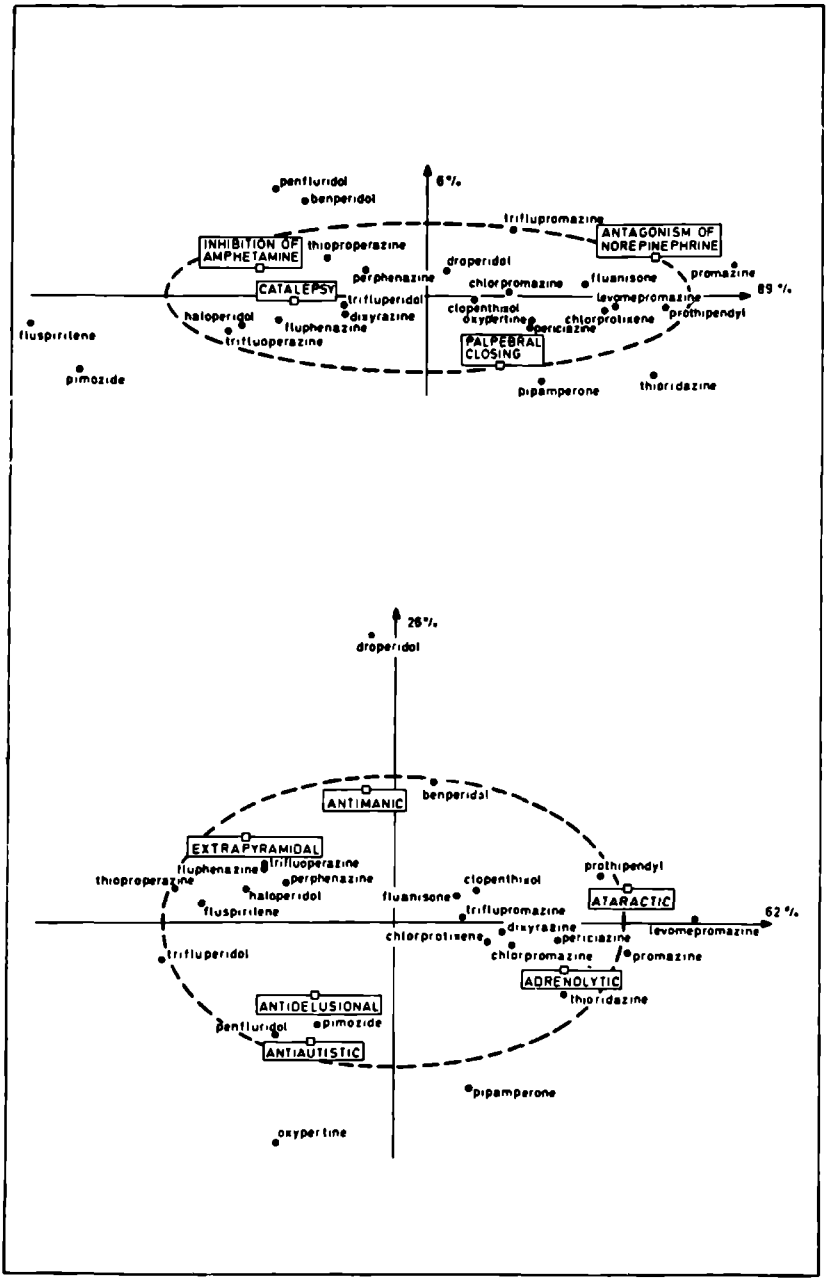


Significant correlations were found between the self-stimulation inhibition and the induction of catalepsy ($r = 0.736$, $p < 0.01$), antagonism of amphetamine ($r = 0.925$, $p < 0.01$) and induction of palpebral ptosis ($r = 0.693$, $p < 0.01$). The self-stimulation inhibition was not significantly correlated with the antagonism of norepinephrine lethality ($r = 0.208$, $p > 0.05$).
It could be inferred that the dopaminergic receptor blocking activity is more specifically related to the self-stimulation inhibition than the noradrenergic receptor blocking effects. Moreover, the doses of the sedative neuroleptics effectively inhibiting self-stimulation block noradrenergic as well as dopaminergic receptors (see e.g. Andén et al., 1970, Table 3).
However, the correlations may also simply reflect the potency-relationships. It is therefore, appropriate to apply a method which separates the potency of neuroleptics from their spectral information.

6.1.2. Spectral map analysis

A technique which separates the potency from the spectral information has been described by Lewi (1976a). In short, spectral map analysis is a mathemathical method, which extracts from the pharmacological data (such as ED_{50}-values of neuroleptic activity in various tests), relevant dimensions which are related to the ratios between the assays. The compounds are projected on a (multi-dimensional) plane and the dominant axes drawn through this plane can be identified with the principal components. The percentage contribution to the total variance of the spectra are calculated. The spectral mapping in a plane thus provides two-dimensional information on the relative positions of the compounds.
Fig. 9 shows the spectral maps (Lewi, 1975b, 1976b) of 24 neuroleptics according to 4 pharmacological assays in rats (Janssen and Van Bever, 1975, see 6.1.1.) and with respect to 6 clinical observations (Bobon et al., 1972).
The pharmacological map shows the more incisive neuroleptics on the left, while more sedative compounds appear on the right. The incisive/sedative ratio of the compounds can be estimated from the relative position of the projections of their images on the map upon the horizontal axis. This axis accounts for about 89 percent of the total information contained in the spectra. The second principal axis contributes no more than 6 percent to the original information.
The clinical map, on the other hand, shows a larger contribution of the minor principal axis, contributing 26 percent. This axis appears to be related to the antimanic/antiautistic differential score. It can be seen that the incisive/sedative classification derived from the horizontal axis of the clinical map agrees with the same classification based on the pharmacological assays in animals. The Spearman rank-order correlation between these two Lambert-type (Lambert and Revol, 1960) classifications is .79.

Fig. 9: Spectral map of various neuroleptics based on pharmacological assays (upper figure) and clinical observations (lower figure) (permission to reprint granted by North-Publishing Company).



6.2. Positioning of psychotropic assays

This method (spectral map analysis) was applied to the neuroleptics tested in self-stimulation and enabled the demonstration of the inter-relationship between the self-stimulation test and other pharmacological assays, such as the tests discussed in the previous section, as well as other tests of operant behaviour. The spectral map analysis was programmed and calculated on an interactive typewriter using APL, a computer language devised by Iverson (1962). The program listings are reported by Lewi (1975a).

Spectral map analysis was carried out on 40 neuroleptics as tested in 12 assays in rats. Two principal components were found, of which the horizontal one accounted for most of the information (73 %). This component reproduced the pharmacological classification described in the previous section, namely the bipolar incisive/sedative scale (Fig. 9).

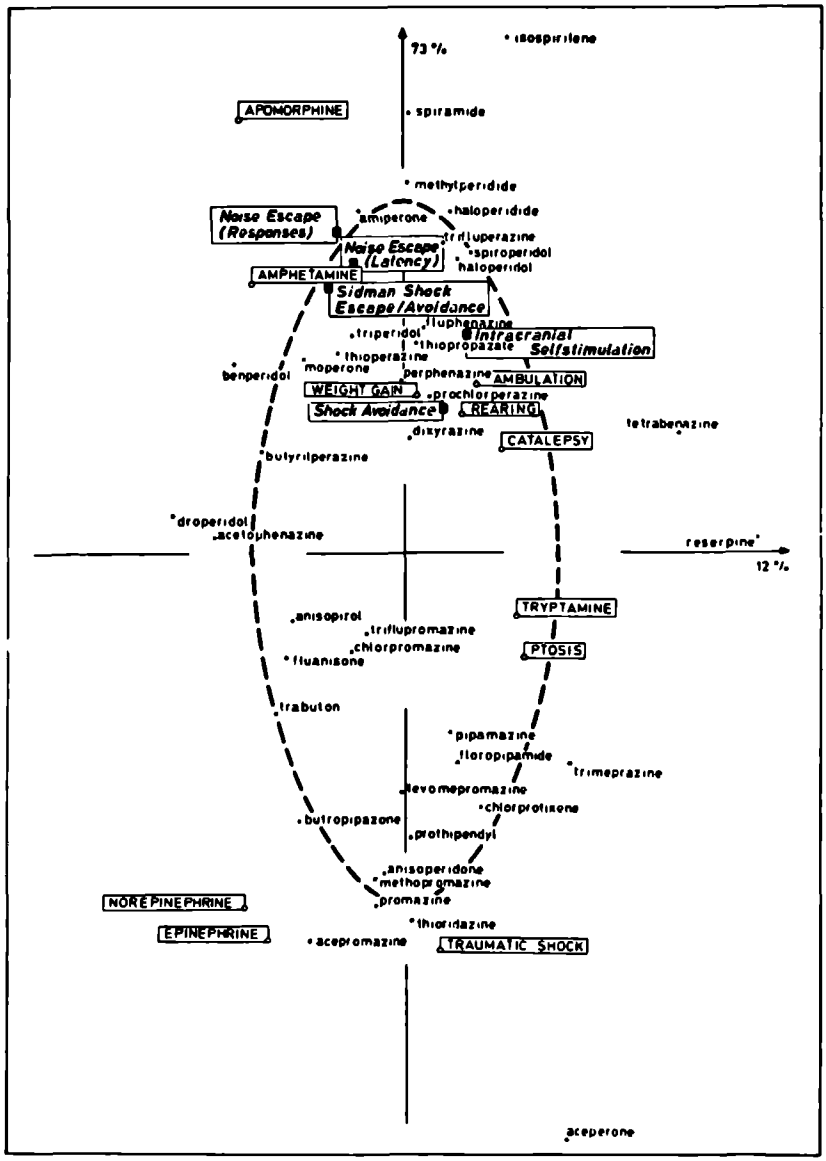
Many neuroleptics were tested in a variety of learned behavioural situations using different schedules in which responding was maintained by negative reinforcement: escape (Niemegeers et al., 1970b, 1972) and avoidance (Janssen and Niemegeers, 1961; Janssen et al., 1965a; Niemegeers, 1974; Niemegeers et al., 1969a, 1969b, 1970a, 1972). The ED_{50}-values of the inhibition obtained with various neuroleptics on brain self-stimulation on the one hand, and various escape or avoidance situations on the other hand, are highly correlated (one example, Sidman shock-avoidance, is given in Table 2). In all these experiments (a) rats learned to press or to jump in order to escape, avoid or obtain reward, (b) well-trained rats and good performers were selected. The situations differed with respect to (a) acquisition rate, (b) training required before stable performance was achieved, (c) motivation (positive versus negative).

The following operant behaviour assays are positioned on the map of neuroleptics (Fig. 10). Noise escape (effects on latency time and on number of responses), Sidman shock escape/avoidance, jumping box shock avoidance and intracranial self-stimulation. It is observed that all these operant behaviour assays are located on a line oriented from apomorphine and amphetamine inhibition towards unrestrained locomotor activity (rearing, ambulation), conditioned feeding (weight gain) and catalepsy. Furthermore, typical escape inhibition is associated most closely with the inhibition of apomorphine and amphetamine, while typical loss of avoidance is most correlated with conditioned and unrestrained activities. Mixed escape/avoidance and intracranial self-stimulation can be seen to occupy intermediate positions between these two extremes. As previously stated (6.1.1.), it appears that the neuroleptic effects on operant behaviour are more related to dopaminergic receptor blocking activity than to the noradrenergic receptor blocking effects. The neuroleptic-induced inhibition of operant behaviour is rather independent of the motivational sign, i.e. reward or aversion.

The intermediate position of the self-stimulation shows the relationship with typical neuroleptic effects and with neurologic side-effects (motor impairment). Common to all these operant behavioural situations is that

they involve complex learned behaviour and involve the occurrence of a reinforcement process. It is suggested that neuroleptics interfere with integrative processes, i.e. interfere with the relationships between behaviour and its consequence.

Fig. 10: Spectral map of various neuroleptics and various operant behaviour assays.



7. STUDIES ON DRUG-INTERACTION

Self-stimulation behaviour depends at least partly, on catecholaminergic and cholinergic interacting functions (Olds and Ito, 1973; Stein, 1968). Olds (1972a) showed that scopolamine (0.5 mg/kg) antagonized about 60 % of the inhibition of self-stimulation induced by chlorpromazine (2.5 mg/kg). The aim of the following studies was to reveal the functional interaction between dopaminergic and cholinergic neurons.

These studies have clinical relevance because of the treatment of Parkinson's disease with drugs which also antagonize the neuroleptic-induced Parkinson-like symptoms; and further, because of the routine combined treatment of neuroleptics with antiparkinsonian agents in psychotic patients.

In all the studies reported in this chapter, we used rats implanted with electrodes in the lateral hypothalamic region of the medial forebrain bundle. Rats were trained in 15- or 30-min daily sessions, using a stimulus parameter combination which elicited high response rates (SPC 6). At least two sessions separated each treatment. The test used to show significant differences between drug-session and control session was the Wilcoxon matched pairs signed-ranks test, two-tailed probability. The level of significance selected was $p < .05$. Further details are reported in the different experiments.

7.1. Literature on neuroleptic-anticholinergic interaction (1)

Relatively few authors studied the interaction between the pharmacological effects of neuroleptics and anticholinergics.

The effects studied were primarily concerned with changes in the extrapyramidal system, both at the behavioural level, e.g. catalepsy (Table 4); and at the biochemical level, e.g. counteraction of the increased levels of homovanillic acid in subcortical brain regions (Andén and Bédard, 1971; Bowers and Roth, 1972; Corrodi et al., 1972; O'Keeffe et al., 1970), and increased rate of dopamine depletion after synthesis inhibition (Puri and Lal, 1973; Puri et al., 1973). Partial blocking of the neuroleptic-induced inhibition of avoidance behaviour has been reported (Table 5). We recently reported on the antagonism of pimozide-induced inhibition of mouse-jumping in amphetamine-dopa treated mice (Colpaert et al., 1975b). It follows that centrally acting anticholinergics are able to antagonize neuroleptic-induced effects. The doses required to antagonize catalepsy or inhibition of avoidance are much higher than those producing central or peripheral anticholinergic activity, as measured in the anti-pilocarpine test in rats (Janssen and Niemegeers, 1967) (Tables 4 and 5).

Quantitative inter-drug comparisons are almost impossible to perform, because of the wide range in activity of the different compounds used, the variable doses, the different injection schedules and routes of administration. It will be shown in the experiments subsequently described that self-stimulation is a reliable means of studying neuroleptic-antagonistic drug interaction.

(1) Partially summarized in Wauquier et al., 1975.

Table 4: Antagonism of neuroleptic-induced catalepsy in rats.

NEUROLEPTICS	Dose mg/kg	Route	Effect (1)	ANTICHOLINERGICS	Dose mg/kg	Route	Effect (1)	ED_{50}=1 (2)	AUTHORS
Chlorpromazine	10.0	s.c.	+++(+)	Ethybenzatropine	1.00	s.c	+(+)	2x	Taeschler et al., 1962
"				"	3.00	s.c.	++	6x	"
"				Scopolamine	0.50	i.p.	+++	31x	Morpurgo & Theobald, 1964
"				Trihexyphenidyl	5.00	i.p.	+++	20x	"
Perphenazine	10.0	i.p.	++++	Atropine	2.00	i.p.	+(+)	8x	Morpurgo, 1962, Morpurgo & Theobald, 1964
"				"	5.00	i.p	+++	21x	"
"				"	10.0	i.p.	+++	42x	"
"				Benztropine	2.00	i.p.	++	8x	"
"				Biperiden	2.00	i.p.	++	-	"
"				Scopolamine	0.10	i.p	+(+)	6x	"
"				"	0.50	i.p.	+++(+)	31x	"
"				"	2.00	i.p.	++++	125x	"
				Trihexyphenidyl	2.00	i.p.	++	8x	Morpurgo, 1962
				"	5.00	i.p	++(+)	20x	Morpurgo & Theobald, 1964
Prochlorperazine	8.00	i.p.	++++	Atropine	11.5	i.p	++	48x	Malatray & Simon, 1972
"				Diethazine	>64.0	i.p	-	-	"
"				Orphenadrine	18.0	i.p	++	0.30	"
"				Procyclidine	14.0	i.p.	++	9.x	"
"				Profenamine	>64.0	i.p.	-	-	"
"				Trihexyphenidyl	9.50	i.p.	++	38.x	"
"				Scopolamine	1.20	i.p.	++	75x	"
Thiopropazate	0.29	s.c.	++	Biperiden	4.00	s.c	++++	-	Schaumann & Kurbjuweit, 1961
"				Chlorphencyclan	0.45	s.c.	+	-	"
Thioproperazine	0.20	i.p.	++	Benztropine	5.00	i p	+++	(21x)	Leslie & Maxwell, 1964
"				Promethazine	12.5	i p	+++(+)	(4x)	"
"				Scopolamine	1.00	i.p.	++++	(62x)	"
Trifluoperazine	10.0	i.p.	++++	Scopolamine	0.50	i.p.	++++	31x	Morpurgo & Theobald, 1964
"				Trihexyphenidyl	5.00	i.p.	++(+)	20x	"

(1) Agonistic effects obtained with neuroleptics and antagonistic effects with anticholinergics expressed as + 25 %, ++ 50 %, +++ 75 %, ++++ 100 %

(2) ED_{50} = Dose of central anticholinergic activity in 50 % of the rats according to Janssen and Niemegeers (1967)

Table 5: Antagonism of neuroleptic-induced inhibition of avoidance in rats.

NEUROLEPTICS	Dose mg/kg	Route	Effect (1)	ANTICHOLINERGICS	Dose mg/kg	Route	Effect (1)	ED_{50}=1 (2)	AUTHORS
Chlorpromazine	2.00	i.p.	+++	Scopolamine	0.20	i.p.	++(+)	12x	Morpurgo & Theobald, 1964
"				Trihexyphenidyl	2.00	i.p.	++(+)	8x	"
Perphenazine	0.20	i.p.	+++	Scopolamine	0.20	i.p.	++(+)	12x	"
"				Trihexyphenidyl	2.00	i p.	++	8x	"
Thiopropazate	0.34	s.c.	++	Biperiden	0.37	s.c.	-	-	Schaumann & Kurbjuweit, 1961
"				Chlorphencyclan	0.86	s.c.	+(+)	-	"
"	1.60	s.c.	++	Biperiden	1.80	s.c.	-	-	"
"				Chlorphencyclan	4.90	s.c.	+(+)	-	"
Thioridazine	1.00	s.c.	0	Ethybenzatropine	0.10	s.c.	0	0.20	Taeschler et al., 1962
"	5.00	s.c.	+(+)	"	0.50	s.c.	++++	1x	"
"	10 0	s.c.	+(+)	"	1.00	s.c.	+++(+)	2x	"
Trifluoperazine	0.40	i.p.	++(+)	Scopolamine	0.20	i p.	++	12x	Morpurgo & Theobald, 1964
"				Trihexyphenidyl	2.00	i p	++++	8x	"

(1) Agonistic effects obtained with neuroleptics and antagonistic effects with anticholinergics expressed as + 25 %, ++ 50 %, +++ 75 %, ++++ 100 %

(2) ED_{50} = Dose of central anticholinergic activity in 50 % of the rats according to Janssen and Niemegeers (1967)

7.2. Reversal of the specific inhibition obtained with anticholinergics

It has been stated (see 6) that specific neuroleptics inhibit self-stimulation by interference with the nigrostriatal system. The latter dopaminergic neurons interact with striatal cholinergic interneurons. Since DA-neural transmission appears to be involved in the neuroleptic-induced inhibition of self-stimulation, one would expect anticholinergics to antagonize the inhibitory effects of specific DA-blocking neuroleptics.

7.2.1. Differentiation from narcotic analgesics (1)

Haloperidol and morphine have a number of similarities: they increase the turnover of striatal DA (Puri and Lal, 1974); they release prolactin (Dickerman et al., 1972); they inhibit the release of luteinizing hormone (Dobrin and Mares, 1974); they produce a state of immobility which can be reversed with apomorphine (Puri et al., 1973). They differ, however, in many respects: haloperidol lacks analgesic effects and tolerance (Lal and Puri, 1973) and neuroleptics cause catalepsy, while morphine-like drugs cause catatonia.

The inhibition of self-stimulation obtained with 0.16 mg/kg of fentanyl or with 40 mg/kg of morphine could not be reversed by the centrally acting anticholinergic dexetimide (2.5 mg/kg) (Tables 6a, b). The associated catatonia was not reversed either. Naloxone on the other hand, reversed the self-stimulation inhibition and catatonia induced by the former drugs. These experiments showed that some actions induced by morphine-like agents are reversed by a specific antagonist. Since DA receptors appear to be involved in causing morphine- or neuroleptic-induced effects, one would expect different mechanisms of action (see also Broekkamp and van Rossum, 1975).

7.2.2. Dose-related antagonism (2)

As shown previously (see 3.2.) a dose of 0.08 mg/kg of haloperidol given s.c., 1 hr before the session, caused a nearly complete suppression of self-stimulation. Dexetimide, a centrally acting anticholinergic (Janssen and Niemegeers, 1967; Janssen et al., 1971), antagonized, in a dose-related manner the suppression of self-stimulation induced by haloperidol.

Eight rats were trained to press a lever for brain-stimulation (SPC 6) in the lateral hypothalamus, during 2 daily 15-min sessions separated by a 4-hr interval. After training they were injected s.c. with 0.08 mg/kg of haloperidol, 1 hr before the first daily session followed 30 min later with either 0.04, 0.16, 0.63 or 2.5 mg/kg of dexetimide s.c. Tables 6a and 6b show the results obtained. Dexetimide gradually reinstated self-stimulation in a dose-related manner. Isopropamide, a peripherally acting anticholinergic drug, at a dose (10 mg/kg) 1000 times higher than those

(1) This study was reported earlier (Wauquier et al., 1974).

(2) This study was reported earlier (Wauquier et al., 1975).

Table 6a: Self-stimulation responses of individual rats, run twice daily, during pre-drug control sessions and after subcutaneous administration of either 1 ml/kg of saline, 0 08 mg/kg of haloperidol, 0 16 mg/kg of fentanyl, 1 hour, before the first session, or 2 5 mg/kg of dexetimide, 1/2 hour before the first session.

Drug treatment	Self-stimulation responses/15 min													
	1st session							2nd session, 4 hrs later						
	Rats #						Median	Rats #						Median
	1	2	3	4	5	6		1	2	3	4	5	6	
Control	383	461	538	627	882	981	582.5	406	441	540	599	900	1018	569.5
Saline	424	379	502	640	879	1078	571.0	400	189	696	572	905	1070	634.0
% change	+10.7	-17.8	-6.69	+2.07	-0.34	+9.89	+0.865	-1.48	-57.1	+28.9	-4.51	+0.56	+5.11	-0.460
Control	275	346	597	645	949	1008	621.0	261	437	567	464	935	1010	515.5
Haloperidol	2	10	133	66	202	117	91.5 *	2	175	669	277	544	938	410.5
% change	-99.3	-97.1	-77.7	-89 8	-78.7	-88.4	- 89.1	-99.2	-60.0	+18.0	-40.3	-41.8	-7.13	-41.05
Control	288	513	577	609	839	973	593.0	317	392	544	441	1041	1039	492.5
Fentanyl	0	0	0	0	0	0	0 *	329	736	557	502	890	981	646.5
% change	-100	-100	-100	-100	-100	-100	-100	+3.79	+87.8	+2.39	+13.8	-14.5	-5.58	+ 3.09
Control	198	441	585	705	1062	1325	645.0	182	465	593	663	1065	1059	628.0
Dexetimide	360	453	487	862	934	1178	674.5	201	517	420	911	1126	737	627.0
% change	+81.8	+2.72	-16.8	+22.3	-12.1	-11.1	- 4.19	+10.4	+11.2	-29.2	+37.4	+5.73	-30.4	+8.065

* Significant difference ($p \leq 05$) between control- and drug session.
Wilcoxon, matched-pairs signed-ranks test, two-tailed probability.

Table 6b: *Self-stimulation response of individual rats, run twice daily, during pre-drug control sessions and after subcutaneous administration of 0.08 mg/kg of haloperidol (Hal) or 0.16 mg/kg of fentanyl (Fen), 1 hour before the first session, followed 1/2 hour later, by either 0.04, 0.16, 0.63 or 2.50 mg/kg of dexetimide (Dex.).*

Self-stimulation responses/15 min														
Compound	1st session						Median	2nd session 4 hrs later						Median
	Rat #							Rat #						
	1	2	3	4	5	6		1	2	3	4	5	6	
Control	275	346	597	645	949	1008	621 0	261	437	567	464	935	1010	515 5
Haloperidol	2	10	133	66	202	117	91.5*	2	175	669	277	544	938	410 5
Control	191	404	634	676	993	1030	655 0	185	403	518	586	911	1044	552 0
Haloperidol (0.08) + Dexetimide (0.04)	55	1	96	135	908	139	115.5*	40	255	381	633	696	1007	507 0
% change	-71.2	-99 8	-84.9	-80.0	-8 56	-86.5	-82 45	-78 4	-36.7	-26.4	+8 02	-23.6	-3.54	- 25.0
Control	242	397	520	596	881	992	558.0	227	347	568	565	903	988	566 5
Haloperidol (0.08) + Dexetimide (0.16)	99	2	344	137	562	115	126.0*	42	373	336	615	952	989	494.0
% change	-59.1	-99.5	-33.8	-77 0	-36.2	-88 4	-68.05	-81.5	+7.49	-40 8	+8.85	+5.43	+0 10	+ 2.77
Control	263	420	595	704	987	1042	649.5	136	315	596	680	935	1003	638 0
Haloperidol (0.08) + Dexetimide (0.63)	231	25	366	586	1029	806	476.0●	127	346	502	609	427	868	464 5
% change	-12.2	-94.0	-38.5	-16 8	+4 26	-22 6	- 19.7	-6 62	+9.84	-15.8	-10.4	-54.3	-13.5	-11 95
Control	209	345	396	581	862	944	488.5	151	279	501	570	809	1024	535.5
Haloperidol (0.08) + Dexetimide (2.5)	241	184	301	511	875	978	406 0●	162	286	485	602	842	934	593 5
% change	+15.3	-46.7	-24.0	12 0	+1 51	+3 60	- 5.25	+7 28	+2.51	+16.8	+5.61	+4.08	-8 79	+ 4 85
Control	288	513	577	609	839	973	593.0	317	392	544	441	1041	1039	492 5
Fentanyl	0	0	0	0	0	0	0*	329	736	557	502	890	981	646 5
Control	319	347	596	628	947	1263	612.0	247	337	596	633	1026	1034	614 5
Fentanyl (0.16) + Dexetimide (2.5)	0	0	0	0	0	0	0*	27	301	737	739	1135	405	571 0
% change	-100	-100	-100	100	-100	-100	-100	-89.1	-10 7	+23 7	+16.7	+10 6	-60 8	- 0.05

* Significant difference ($p < .05$) between control- and drug session.

● Significant difference ($p < .05$) between haloperidol- or fentanyl-treatment and combined treatment.

Wilcoxon matched-pairs signed-ranks test, two-tailed probability

producing peripheral anticholinergic activity (Janssen and Niemegeers, 1967), did not antagonize the haloperidol-induced inhibition.
The reversal of the inhibition by dexetimide suggests that the haloperidol-effect was due to some altered relationship between dopaminergic and cholinergic activity in striatum (Klawans, 1973; Sigwald, 1971), either by cholinergic inhibition or dopaminergic stimulation.
In the following studies, we selected the dose of 0.63 mg/kg of dexetimide, because this was the lowest dose to reverse more than 50 % of the haloperidol-induced inhibition.

7.2.3. Antiparkinsonian drugs

The reversal of the haloperidol-induced inhibition of self-stimulation was not an exclusive action of dexetimide. Benztropine (10 mg/kg) likewise antagonized the inhibition brought about by haloperidol (Wauquier et al., 1974).
In another study we compared the antagonism of the penfluridol- and clopimozide-induced inhibition by three antiparkinsonian agents; dexetimide, benztropine and trihexyphenidyl.
Seven rats were trained to self-stimulate for SPC 6 in daily 30-min sessions, 5 days a week, except for Monday when they were run twice, with a 4-hr interval between the sessions. A dose of the long-acting neuroleptics penfluridol (5 mg/kg) (Janssen et al., 1970) and clopimozide (1.25 mg/kg) (Janssen et al., 1975a) which, as described, suppressed self-stimulation virtually completely, was given orally 1 hr before the first session on Monday. During subsequent weeks rats were treated with the neuroleptic followed 4 hrs later, i.e. 1 hr before the second session on Monday, with either dexetimide (0.63 mg/kg), benztropine (10 mg/kg) or by trihexyphenidyl (10 mg/kg) s.c. Rats were only treated once per week. Tables 7a, b and Fig. 11 depict the results obtained.
At the doses used, penfluridol and clopimozide significantly inhibited self-stimulation 4 hrs, 24 hrs and 48 hrs after injection. The inhibition was most pronounced 4 hrs after neuroleptic treatment and self-stimulation gradually recovered during the following 4 days. The three antiparkinsonian drugs, which by themselves did not significantly affect self-stimulation, completely reversed the self-stimulation inhibition obtained 4 hrs after neuroleptic treatment. Self-stimulation was completely normalized (not significantly different from controls) except for the combination of penfluridol with trihexyphenidyl. However, during the following days, self-stimulation rates did not differ from the rates obtained after neuroleptic treatment alone.
This study showed that the self-stimulation inhibition induced by specific neuroleptics could be reversed by three different antiparkinsonian drugs at a time when maximum inhibition could be expected.
Whether the anticholinergics were specific with respect to the reversal of the self-stimulation inhibition is still a matter of debate.

Fig. 11: Median self-stimulation response rates as a percentage of control values obtained with 7 rats, 1 hr, 4 hrs, 24 hrs, 48 hrs, 72 hrs and 96 hrs after oral administration of 5 mg/kg of penfluridol (1) (upper) or 1.25 mg/kg of clopimozide (1) (lower) or, after combined treatment with either penfluridol or clopimozide, plus 0.63 mg/kg of dexetimide (2), 10 mg/kg of benztropine (3) or 10 mg/kg of trihexyphenidyl (4). The latter antiparkinsonian drugs were given s.c. 1 hr before the 4-hr session.

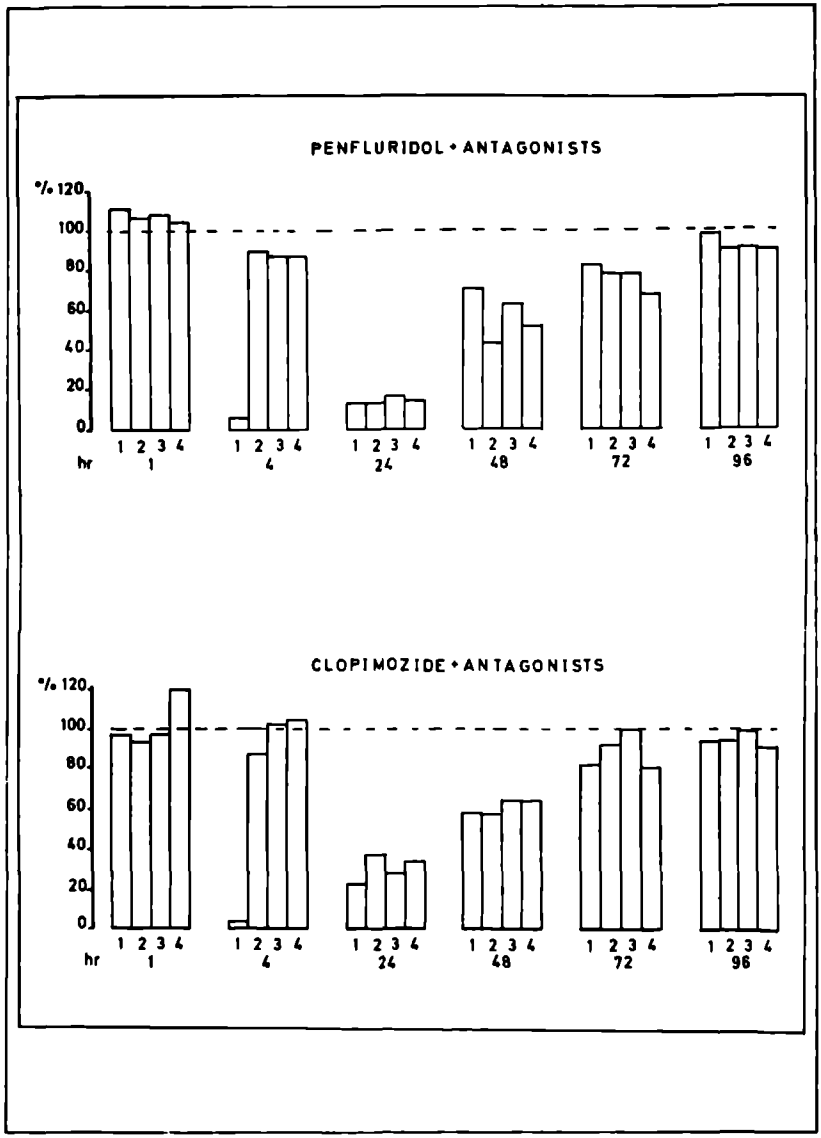


Table 7a: *Self-stimulation response rates of 7 rats run 1 hr, 4 hrs, 24 hrs, 48 hrs, 72 hrs and 96 hrs after oral administration of water, penfluridol or the combination of penfluridol with either dexetimide, benztropine or trihexyphenidyl given s.c. 3 hrs after penfluridol.*

Compounds	Hr	Rat #							Median
		1	2	3	4	5	6	7	
Saline sessions	1	1390	1051	2150	1991	1085	787	859	1085
	4	1465	1299	1896	2077	965	978	939	1299
	24	1416	1314	2260	1883	974	839	1049	1314
	48	1400	1553	2126	2221	1092	939	1038	1400
	72	1449	1145	2198	1862	1225	1016	1063	1225
	96	1433	1629	2166	2198	1225	916	1029	1433
Penfluridol	1	1377	1291	2377	2103	765	890	1312	1312
5 mg/kg or.	4	23	5	971	110	52	11	64	52*
	24	182	173	1389	280	416	63	134	182*
	48	1265	78	1680	1588	767	407	148	767*
	72	1310	700	1982	2227	775	700	881	881
	96	1458	736	2440	2170	907	962	971	971
Penfluridol	1	1539	1039	1832	2107	931	884	1086	1086
5 mg/kg or.	4	1200	841	1927	1861	1189	1210	707	1200 (*)
+	24	125	67	1400	251	221	184	54	184*
Dexetimide	48	597	33	1125	1729	705	147	43	597*
0.63 mg/kg s.c. (+ 3 hrs)	72	1204	630	1727	1133	970	796	15	970*
	96	1373	658	2276	1986	1099	738	870	1099*
Penfluridol	1	1534	390	2292	2147	1148	962	1096	1148
5 mg/kg or.	4	1265	481	1800	1047	677	893	1134	1047 (*)
+	24	234	153	1333	148	171	197	95	171*
Benztropine	48	1217	70	1495	1434	684	480	49	684*
10 mg/kg s.c. (+ 3 hrs)	72	1182	72	1721	1844	851	928	308	928*
	96	1253	821	1964	2163	1140	1104	751	1140
Penfluridol	1	1530	913	1262	2072	1029	857	1157	1157
5 mg/kg or.	4	1364	715	1774	1162	831	1031	613	1031 *(*)
+	24	203	97	1566	509	147	115	39	147*
Trihexyphenidyl	48	863	632	1558	1398	559	208	72	632*
10 mg/kg s.c. (+ 3 hrs)	72	996	1140	1800	1984	815	74	561	996*
	96	1288	1153	2064	1971	1145	897	764	1153*

* Significant difference ($P < 0.05$) from saline sessions.

(*) Significant difference ($P < 0.05$) from penfluridol treatment (Wilcoxon matched-pairs signed-rank test, two-tailed probability).

Table 7b: Self-stimulation response rates of 7 rats run 1 hr, 4 hrs, 24 hrs, 48 hrs, 72 hrs and 96 hrs after oral administration of water, clopimozide or the combination of clopimozide with either dexetimide, benztropine or trihexyphenidyl given s.c. 3 hrs after clopimozide.

Compounds	Hr	Rat #							Median
		1	2	3	4	5	6	7	
Saline sessions	1	1580	1611	2071	2180	1153	1032	1060	1580
	4	1458	1727	1951	1447	1347	910	793	1447
	24	1536	1494	2021	1894	1384	1099	881	1494
	48	1661	1052	1885	2192	1139	1078	1047	1139
	72	1333	1274	2021	2262	1117	1032	1141	1274
	96	1412	1383	2021	2140	1202	926	1145	1383
Clopimozide 1.25 mg/kg or.	1	1523	1779	1925	2152	967	704	1101	1523
	4	42	60	687	101	15	0	115	60*
	24	325	504	1430	718	313	103	152	325*
	48	128	976	1439	1745	663	694	69	694*
	72	977	1468	1655	2302	972	845	279	977
	96	1158	1259	1904	2255	1205	877	765	1205
Clopimozide 1.25 mg/kg or. + Dexetimide 0.63 mg/kg s.c. (+ 3 hrs)	1	1450	1479	2047	1798	1249	906	1274	1450
	4	1712	1452	1677	1193	322	1271	880	1271 (Ⓢ)
	24	414	785	1630	779	204	99	330	414*
	48	543	934	1619	1734	641	225	556	641*
	72	1072	1320	1906	2200	1033	865	503	1072*
	96	1094	1304	1889	2158	1257	1197	648	1257
Clopimozide 1.25 mg/kg or. + Benztropine 10 mg/kg s.c. (+ 3 hrs)	1	1838	2223	1841	1849	1120	931	1341	1838
	4	1836	1739	1876	575	273	1265	1239	1265 (Ⓢ)
	24	233	577	1055	411	53	99	238	238*
	48	370	1330	1629	1613	691	690	344	691*
	72	1078	1713	2011	1968	1301	910	1251	1301
	96	1509	1981	1844	2125	1499	926	1098	1509
Clopimozide 1.25 mg/kg or. + Trihexyphenidyl 10 mg/kg s.c. (+ 3 hrs)	1	1885	2573	1872	1930	1445	986	1368	1872
	4	1699	1795	1977	320	904	1235	1006	1235 (Ⓢ)
	24	518	889	1194	637	71	353	286	518*
	48	450	671	1312	1684	801	457	137	671*
	72	1318	958	952	1823	1360	922	773	958
	96	1208	1968	1826	1970	1526	950	820	1526

* Significant difference ($P < 0.05$) from saline sessions.

Ⓢ Significant difference ($P < 0.05$) from clopimozide treatment (Wilcoxon matched-pairs signed-rank test, two-tailed probability).

7.3. Differential antagonism

In as much as DA-neural transmission is involved in the antagonism by antiparkinsonian drugs of neuroleptic-induced inhibition, one would expect anticholinergics to antagonize the inhibitory effects of specific DA-blocking neuroleptics, without affecting the inhibition brought about by NA-blocking neuroleptics.
Further, different mechanisms could account for the reversal of the inhibition: anticholinergic activity, release of DA-uptake blocking activity and so forth. It was the aim of the following studies to elucidate the possible mechanism involved, by using various putative antagonists.

7.3.1. Differential antagonism between the neuroleptics

7.3.1.1. (1) Three different neuroleptics were selected: pimozide, haloperidol and pipamperone. Pimozide and haloperidol, are both specific DA-blocking neuroleptics; haloperidol, however, also blocks NA-receptors at high dose-levels. Pipamperone, on the contrary, blocks DA and NA receptors at approximately the same dose-levels (Andén et al., 1970) (see 6). Four doses of each neuroleptic were given, the second dose being approximately the ED_{50}-value for inhibition, the fourth dose being 16 times higher. All rats were also given the combination of the neuroleptic and 0.63 mg/kg of dexetimide. Tables 8a, b, c and Fig. 12 show the results obtained.
Dexetimide completely reversed the self-stimulation inhibition induced by pimozide and self-stimulation was normalized to control levels. The haloperidol-induced inhibition was significantly antagonized at all dose-levels, but self-stimulation was not normalized to control levels with the combination of dexetimide with 0.16 mg/kg and 0.63 mg/kg of haloperidol. The pipamperone-induced inhibition was not antagonized by dexetimide.
The inhibition of self-stimulation induced by pimozide and haloperidol is probably due to the DA-blocking activity, whereas the pipamperone-induced inhibition is related to the DA- and NA-blocking activity. It follows that dexetimide reversed the DA-blocking effect, whereas the NA-blocking effect would not be antagonized. The latter had to be evidenced further by using different neuroleptics, which preferentially block NA receptors.

7.3.1.2. A group of rats was treated with various sedative neuroleptics (ratio NE/AM lower than 1, see 6.1.) and a combination of these neuroleptics with 0.63 mg/kg of dexetimide. The neuroleptics were: azaperone (2.5 mg/kg), chlorpromazine (2.5 mg/kg), chlorprotixene (2.5 mg/kg), clozapine (40 mg/kg), haloanisone (2.5 mg/kg), oxypertine (10 mg/kg), piperazetacine (0.63 mg/kg), promazine (40 mg/kg) and thioridazine (40 mg/kg). The dose of the neuroleptic was the first one of a geometrical series (0.04, 0.08, ... 40 mg/kg of body weight) completely inhibiting self-stimulation (based on 3.2.2. and pilot experiments).

(1) This study was reported earlier (Wauquier and Niemegeers, 1975).

Fig. 12: Self-stimulation in rats: median (8 rats) response rate expressed as a percentage of the preceding control (= 100 %) obtained after neuroleptic (▨) and combined neuroleptic-anticholinergic treatment (■). (Permission to reprint granted by Arch. int. Pharmacodyn. Ther.).

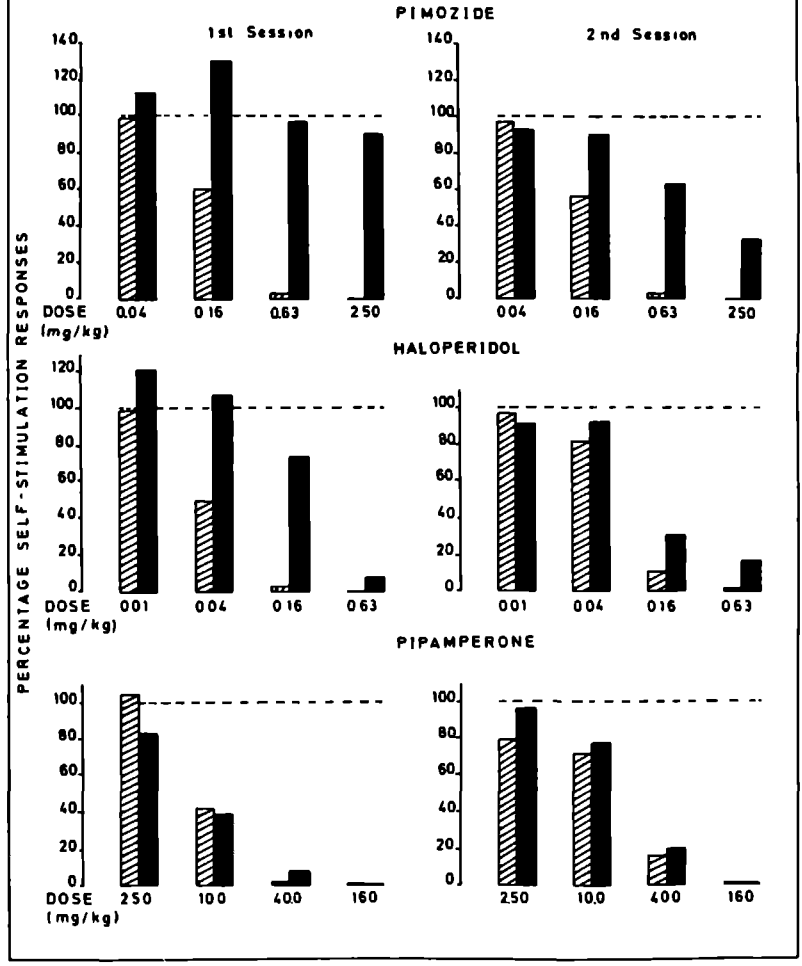


Table 8a: *Self-stimulation response rates of 8 rats, run twice daily (4-hour interval), after subcutaneous administration of saline (1 ml/kg) or different doses of pimozide and the combination of pimozide, given 2 hrs, and dexetimide, given 1/2 hr before the first session.*

	Compounds	Dose mg/kg	Rat # 1	2	3	4	5	6	7	8	Median
First daily session	Saline sessions preceding pimozide doses	0	1284	1816	433	1450	1669	923	2607	696	1367
		0	1575	1460	1347	1170	1783	1245	1953	1322	1404
		0	1686	1504	1439	2286	1545	1166	2630	897	1525
		0	1390	1665	1461	1189	1678	1068	2641	809	1426
	Pimozide alone	0.04	1174	1678	459	1612	968	1099	2729	542	1137
		0.16	612	79	849	1418	150	887	1117	1105	868 (1)
		0.63	183	0	10	261	33	19	256	34	33.5(2)
		2.50	18	0	3	5	5	33	41	0	5 (2)
	Saline sessions preceding pimozide dose + dexetimide 0.63 mg/kg	0	1433	1750	776	1401	1608	1056	2838	598	1417
		0	816	964	1399	1301	1257	1136	1400	1202	1230
		0	1580	1387	1590	2268	894	1002	2885	703	1484
		0	991	1622	1362	1390	1326	809	2061	569	1344
	Pimozide doses + Dexetimide 0.63 mg/kg	0.04	1470	1923	1434	1985	1464	1224	3013	1149	1467(1)
		0.16	1574	900	1824	1915	1655	1329	1837	1475	1615(1)
		0.63	1837	1426	1509	2154	702	986	1689	699	1468
		2.50	1334	658	1334	1868	1099	797	1227	421	1163
Second daily session	Saline sessions preceding pimozide doses	0	1495	1625	231	1341	1730	967	2787	758	1418
		0	1412	1385	1472	1317	1707	1148	1902	1162	1399
		0	1547	1505	1207	2282	1520	1199	2589	702	1513
		0	1459	1617	1489	1070	1616	1108	2676	721	1474
	Pimozide alone	0.04	1382	1645	612	1514	988	1152	2547	597	1267
		0.16	1275	539	560	1698	151	888	1192	593	740.5(1)
		0.63	37	1	0	701	32	204	151	2	34.5 (2)
		2.50	12	1	3	0	15	7	32	0	5 (2)
	Saline sessions preceding pimozide dose + dexetimide 0.63 mg/kg	0	1505	1820	784	1701	1628	1111	3102	559	1567
		0	666	1450	1413	1337	1506	1148	1920	1203	1375
		0	1616	1516	1680	2471	1184	986	2633	795	1566
		0	1405	1530	1518	1483	1287	950	2271	549	1444
	Pimozide doses + Dexetimide 0.63 mg/kg	0.04	1392	1756	941	1427	1311	829	2862	593	1352
		0.16	979	1075	758	1361	1424	987	1505	1268	1172
		0.63	1067	901	421	1738	1110	919	1256	274	993 (2)
		2.50	1279	135	79	1831	465	494	402	162	433.5(1)

(1) Significant difference between drug-session and preceding control session at the level of $P < .05$ (Wilcoxon matched-pairs signed-rank test, two-tailed probability).
(2) $P < .01$

Table 8b: *Self-stimulation response rates of 8 rats, run twice daily (4-hour interval), after subcutaneous administration of saline (1 ml/kg) or different doses of haloperidol and the combination of haloperidol, given 1 hr, and dexetimide, given 1/2 hr before the first session.*

	Compounds	Dose mg/kg	Rat # 1	2	3	4	5	6	7	8	Median
First daily session	Saline sessions preceding haloperidol doses	0	863	878	912	1162	1780	1330	1971	596	1037
		0	1663	1248	1338	2862	1731	1045	2616	965	1501
		0	1413	1576	514	1570	1821	923	2528	925	1492
		0	1380	981	1443	1476	1609	1072	2047	850	1412
	Haloperidol alone	0.01	631	606	1154	1434	1913	1225	2093	459	1190
		0.04	1383	1049	179	164	44	799	1815	281	540 (2)
		0.16	53	14	21	88	17	153	94	0	37 (2)
		0.63	0	4	1	0	0	14	16	0	0.5 (2)
	Saline sessions preceding haloperidol dose + dexetimide 0.63 mg/kg	0	1361	1562	985	1140	1813	1332	1983	642	1347
		0	1610	1356	1546	2348	1625	908	2679	801	1578
		0	1333	1301	364	1926	1956	674	2842	896	1317
		0	1529	1292	1421	1345	1732	1080	2780	902	1383
	Haloperidol doses + Dexetimide 0.63 mg/kg	0.01	1494	1417	1422	2016	2123	1680	1860	1461	1587
		0.04	1656	1288	1824	2598	1256	1260	2354	1476	1566
		0.16	981	431	208	1416	1438	752	2481	133	866.5(1)
		0.63	454	48	64	142	37	170	291	14	103 (2)
Second daily session	Saline sessions preceding haloperidol doses	0	1071	1074	1155	1217	1739	1404	2287	589	1186
		0	1658	1094	1509	2811	1555	1075	2744	973	1532
		0	1294	1495	508	1541	1854	774	2590	788	1395
		0	1544	1329	1347	1292	1464	1045	2007	807	1338
	Haloperidol alone	0.01	541	444	1092	1307	1850	1368	2226	651	1200
		0.04	1623	1307	1148	939	50	1108	2397	604	1128
		0.16	274	1276	5	16	0	817	540	2	145 (1)
		0.63	20	0	12	284	2	8	4	0	6 (2)
	Saline sessions preceding haloperidol dose + dexetimide 0.63 mg/kg	0	1338	1302	1596	1411	1886	1255	1874	675	1375
		0	1434	1237	1147	2344	1629	922	2526	893	1336
		0	1672	1893	493	1677	1907	505	2833	795	1675
		0	1519	1440	1682	1194	1507	1099	2752	802	1474
	Haloperidol doses + Dexetimide 0.63 mg/kg	0.01	1279	724	802	1410	1773	1333	1632	297	1306 (1)
		0.04	1640	359	1080	2123	1429	953	2493	812	1255
		0.16	177	1369	152	1603	583	822	384	211	483.5(1)
		0.63	1015	49	405	127	334	52	738	5	230.5(2)

(1) Significant difference between drug-session and preceding control session at the level of $P < .05$ (Wilcoxon matched-pairs signed-rank test, two-tailed probability).
(2) $P < .01$

Table 8c: Self-stimulation response rates of 8 rats, run twice daily (4-hour interval), after subcutaneous administration of saline (1 ml/kg) or different doses of pipamperone and the combination of pipamperone, given 1 hr, and dexetimide, given 1/2 hr before the first session.

	Compounds	Dose mg/kg	Rat # 1	2	3	4	5	6	7	8	Median
First daily session	Saline sessions preceding pipamperone doses	0	579	700	1377	1750	1498	958	603	729	843.5
		0	1522	1297	518	1515	1470	1076	2850	598	1384
		0	1779	1122	1338	1139	1482	1291	1599	1167	1315
		0	1589	1754	1147	1288	722	809	2093	870	1218
	Pipamperone alone	2.50	1010	1097	1255	1751	1087	931	1094	793	1091
		10.0	1256	687	74	1259	77	338	1880	0	512.5(2)
		40.0	226	15	0	6	3	29	70	0	10.5 (2)
		160	23	18	0	14	0	0	0	0	0 (2)
	Saline sessions preceding pipamperone dose + dexetimide 0.63 mg/kg	0	1687	893	1379	1667	1632	1028	2651	529	1506
		0	1319	1555	479	1527	1846	1095	2936	422	1423
		0	1653	1468	1505	1161	1266	1421	1828	921	1445
		0	1367	1765	1646	1189	989	892	1973	736	1278
	Pipamperone doses + Dexetimide 0.63 mg/kg	2.50	910	779	1086	1842	1231	914	1571	1087	1087
		10.0	83	493	80	1047	929	504	1837	91	498.5(2)
		40.0	249	95	1	177	16	56	156	259	125.5(2)
		160	0	0	0	0	0	0	0	0	0 (2)
Second daily session	Saline sessions preceding pipamperone doses	0	1331	993	1576	1907	1581	1006	953	1312	1322
		0	1477	1437	559	1446	1711	1167	2749	586	1442
		0	1967	1486	1431	1425	1543	1250	1825	1034	1459
		0	1588	1461	1268	1215	990	797	2056	897	1242
	Pipamperone alone	2.50	666	1266	1191	1868	1247	810	973	666	1082
		10.0	1020	1062	281	1419	1302	617	2290	320	1041 (2)
		40.0	223	0	432	296	2	323	964	60	259.5(2)
		160	0	0	0	0	0	0	0	0	0 (2)
	Saline sessions preceding pipamperone dose + dexetimide 0.63 mg/kg	0	1789	1050	1408	1514	1636	1026	2544	607	1461
		0	1270	1736	488	1552	1864	1112	2798	461	1411
		0	1748	1324	1533	1492	1681	1340	2205	722	1513
		0	1405	1750	1637	1136	894	826	1951	773	1271
	Pipamperone doses + Dexetimide 0.63 mg/kg	2.50	1685	1187	1583	1482	1408	740	2058	1313	1445
		10.0	1188	1097	57	1584	1394	579	2247	414	1143 (1)
		40.0	400	44	1268	1451	0	226	371	401	385.5(2)
		160	0	0	0	0	0	0	0	0	0 (2)

(1) Significant difference between drug-session and preceding control session at the level of $P < .05$ (Wilcoxon matched-pairs signed-rank test, two-tailed probability).
(2) $P < .01$

The inhibition of self-stimulation induced by these neuroleptics was not reversed by dexetimide, except for thioridazine (see further 7.4).
The self-stimulation inhibition is probably due to its NA-blocking and DA-blocking activity. Dexetimide could reverse the DA-blocking effect completely (as was shown for pimozide) but because of the NA-blocking effect, self-stimulation remained inhibited.

7.3.2. Specificity of the antagonists

Sedative neuroleptics could not be antagonized with the anticholinergic dexetimide, while specific neuroleptics were. Most anticholinergics, however, also inhibit the neuronal uptake of DA (e.g. Coyle and Snyder, 1969). Dopamine-uptake blockers therefore, could be potential antagonists of incisive neuroleptics. Further, amphetamine which releases DA and NA, could probably reverse to a certain extent the inhibition brought about by sedative neuroleptics, as well as, incisive neuroleptics.
Firstly, different compounds which interact with DA- or NA-transmission were used as antagonists of the self-stimulation inhibition induced by pimozide. These were amphetamine (release of DA and NA), apomorphine and piribedil (DA receptor stimulating agents); cocaine and nomifensine (DA-uptake blocking agents); desipramine (NA-uptake blocking drug) and dexamisole (amine-uptake blocker, Vanhoutte and Van Nueten, 1975).
Secondly, four sedative neuroleptics, i.e. chlorpromazine, pipamperone, clozapine and thioridazine were challenged with dexetimide (see 7.2), amphetamine and nomifensine.
All experiments were carried out with rats self-stimulating for SPC 6 on daily half-hour sessions. Drug-treatment was randomized in each individual rat, but single treatment always preceded combined treatment.
The results of the first experiment are given in Table 9. The antagonistic drugs, at the doses used, did not significantly affect self-stimulation, except for apomorphine, which caused a slight inhibition. The two DA-receptor stimulating drugs apomorphine and piribedil, did not antagonize the pimozide-induced inhibition; neither did desipramine.
Amphetamine on the other hand, significantly antagonized the inhibition of self-stimulation but a large inter-individual variation was found. Cocaine, as well as nomifensine, significantly antagonized the inhibition of self-stimulation. With nomifensine, self-stimulation was completely normalized.
The results of the second experiment are shown in Tables 10a, b, c and Fig. 13. The pimozide-induced inhibition was significantly antagonized with dexetimide, amphetamine and nomifensine. Self-stimulation rates were not normalized with amphetamine, whereas they were after dexetimide and nomifensine.
Amphetamine and nomifensine completely normalized self-stimulation after chlorpromazine treatment. A very slight antagonism was found with dexetimide. Very little antagonism of the pipamperone-induced inhibition was found with dexetimide and amphetamine. The clozapine-induced inhibition was slightly antagonized with amphetamine.

Table 9: Self-stimulation responses of individual rats, obtained during pre-drug sessions and after subcutaneous administration of either 1 ml/kg of saline or indicated compounds (left) or after 0.63 mg/kg of pimozide, 2 hrs before the session, followed 1 1/2 hr later by either nomifensine (2.5 mg/kg), cocaine (10 mg/kg), amphetamine (0.63 mg/kg), dexamisole (10 mg/kg), apomorphine (0.31 mg/kg), piribedil (10 mg/kg) or desipramine (10 mg/kg).

Self stimulation responses/30 min												Self stimulation responses/30 min										
Drug treatment (mg/kg)		Rat #									Median	Drug treatment (mg/kg)		Rat #								Median
		1	2	3	4	5	6	7	8	9				1	2	3	4	5	6	7	8	9	
Control	C_1	1482	992	993	712	828	999	1674	1104	1948	999	Control	C	1456	1269	1185	733	732	1014	1402	1862	1993	1269
Saline	C_2	1548	1299	1136	705	707	928	1410	1029	1834	1136	Pimozide (0.63)	R	365	67	97	204	14	76	109	76	35	76 *
%	C_1/C_2	104	131	114	99 0	85 4	92 9	90 2	91 2	94 3	94 3	%	C R	25 1	5 28	8 19	27 8	1 91	7 40	7 77	4 08	1 76	7 50
Control	C	1236	1710	1133	1929	2645		641		1667	1667	Control	C	1484	1617	1346	1843	2530		381		1478	1478
Nomifensine (2.5)	R	2104	1691	1131	1918	2798		784		1439	1691	Pimozide (0 63) + Nomifensine (2.5)	R	2164	1944	1334	1085	2723		61		2146	1944 @
%	C/R	170	98 9	99 8	99 4	106		122		86 3	99 8	%	C R	146	120	99 1	58 9	108		16 0		136	108
Control	C	1696	975	748	1072		993	1218	1305	1712	1145	Control	C	1733	1471	1075	1023		1227	1262	987	1793	1244 *
Cocaine (10)	R	2248	1776	1460	856		1164	1191	1146	1499	1325 *	Pimozide (0.63) + Cocaine (10)	R	1675	1345	1012	732		1031	1317	731	1478	1074 *@
%	C/R	134	182	195	79 9		117	97 8	87 8	87 6	107 4	%	C R	96 7	91 1	96 0	71 n		84 0	88 5	74 1	88 0	88 25
Control	C	1798	618	1190	1054	983	1480	1475	667	1480	1190	Control	C	1582	820	1000	1238	794	1578	1232	700	1645	1232
Amphetamine (0.63)	R	2058	859	1405	827	1196	1340	1141	510	1492	1340	Pimozide (0 63) + Amphetamine (0.63)	R	571	1182	772	222	146	100	737	52	1341	571 *@
%	C/R	114	139	118	78 4	142	84 8	77 4	76 4	94 4	94 4	%	C R	36 1	144	70 8	17 9	18 4	6 34	59 8	7 43	81 5	36 1
Control	C	1989	1405	1169	732	1202	1105	974	898	1150	1150	Control	C	1862	1394	1321	854	807	957	1073	907	2030	1073
Dexamisole (10)	R	2022	321	1268	336	1237	908	760	505	1787	908	Pimozide (0 63) + Dexamisole (10)	R	1062	451	914	526	27	526	218	255	209	451 *@
%	C/R	102	22 8	108	47 1	101	82 2	77 0	56 2	155	82 2	%	C R	57 3	32 4	69 2	61 5	3 35	55 0	20 3	28 1	10 3	32 4
Control	C	1514	1270	1184	1049		989	1444	760	1737	1227	Control	C	1198	1292	1418	996		1045	1040	954	1606	1168 *
Apomorphine (0.31)	R	424	70	734	1370		889	1260	279	994	811 *@	Pimozide (0 63) + Apomorphine (0 31)	R	223	563	324	56		49	11	132	344	177 *@
%	C/R	28 0	5 51	62 0	131		89 9	87 5	36 7	57 2	59 6	%	C R	16 0	42 8	22 8	5 62		4 69	1 06	13 8	21 4	14 9
Control	C	25 7	816	1528		433	1592				1428	Control	C	2542	909	1643		482	1716				1643
Piribedil (10)	R	1829	806	1710		383	1767				1710	Pimozide (0 63) + Piribedil (10)	R	276	76	199		1	355				199 *@
%	C/R	71 5	98 8	112		88 5	111				98 8	%	C R	10 9	8 36	12 1		0 62	20 7				10 9
Control	C	1222	1277	1456		724	1246				1246	Control	C	2068	1251	2012		550	1524				1524
Desipramine (40)	R	170	323	1415		667	1490				667	Pimozide (0 63) + Desipramine (40)	R	50	25	14		0	166				25 *@
%	C/R	13 9	25 3	104		92 1	120				92 1	%	C R	2 42	2 00	0 70		0	10 9				2 00

* Significant difference ($p < .05$) between control- and drug session.

@ Significant difference ($p < .05$) between pimozide-treatment and combined treatment.

Wilcoxon matched-pairs signed-ranks test, two-tailed probability

Table 10a: *Self-stimulation responses of individual rats, obtained during pre-drug control sessions (C) and after administration of either pipamperone (40 mg/kg), clozapine (40 mg/kg), thioridazine (40 mg/kg) or chlorpromazine (2.5 mg/kg), 1 hr before the session or these compounds followed 1/2 hr later by 0.63 mg/kg of dexetimide. All compounds were given subcutaneously, except clozapine, which was given orally.*

Self-stimulation responses/30 min										
Compound	Dose mg/kg		Rat #							Median
			1	2	3	4	5	6	7	
Pipamperone	40	C	1779	1122	1338	1139	1482	1291	1167	1291
		R	226	15	0	6	3	29	0	6 *
%		C/R	12.7	1.34	0	0.527	0 202	2.25	0	0.527
+ Dexetimide	0.63	C	1653	1468	1505	1161	1266	1421	921	1421
		R	249	95	1	177	16	56	259	95 * Ⓢ
%		C/R	15.1	6.47	0.066	15.2	1.26	3.94	28.1	6.47
Clozapine	40	C	1504	938	1546	1255	976	1267	536	1255
		R	34	4	0	0	0	0	0	0 *
%		C/R	2.26	0.426	0	0	0	0	0	0
+ Dexetimide	0.63	C	1470	1251	1797	1110	1564	1092	433	1251
		R	85	225	0	178	0	0	0	0 *
%		C/R	5.78	18.0	0	16.0	0	0	0	0
Thioridazine	40	C	1255	1550	726	1164	2095	1062	658	1164
		R	19	43	32	9	247	525	271	43 *
%		C/R	1.51	2.77	4.41	0.773	11.8	49.4	41.2	4.41
+ Dexetimide	0.63	C	1560	1123	1261	1314	2206	1100	788	1261
		R	1172	912	1266	1548	1790	659	367	1172 Ⓢ
%		C/R	75.1	81.2	100.4	118	81.1	59 9	46 6	81.1
Chlorpromazine	2.5	C	645	2612	1613	598	1443	1470	1501	1470
		R	1	33	90	3	104	26	0	26 *
%		C/R	0.155	1.26	5.58	0.502	7.21	1.77	0	1.26
+ Dexetimide	0.63	C	694	2677	1549	405	1429	1476	1066	1429
		R	61	359	3	2	20	217	115	61 *
%		C/R	8.79	13.4	0.194	0.494	1.40	14 7	10.8	8 79

* Significant difference ($p < .05$) between control- and drug session.

Ⓢ Significant difference ($p < .05$) between neuroleptic-treatment and combined neuroleptic-dexetimide treatment.

Wilcoxon matched-pairs signed-ranks test, two-tailed probability.

Table 10b: *Self-stimulation responses of individual rats, obtained during pre-drug control sessions (C) and after administration of either pipamperone (40 mg/kg), clozapine (40 mg/kg), thioridazine (40 mg/kg) or chlorpromazine (2.5 mg/kg), 1 hr before the session or these compounds followed 1/2 hr later by 0.63 mg/kg of amphetamine. All compounds were given subcutaneously, except clozapine, which was given orally.*

Self-stimulation responses/30 min										
Compound	Dose mg/kg		Rat #							Median
			1	2	3	4	5	6	7	
Pipamperone	40	C	1338	1291	1779	1139	1482	1338	1122	1338
		R	0	29	226	6	3	0	15	6 *
%		C/R	0	2.25	12.7	0.527	0.202	0	1.34	0.527
+ Amphetamine	0.63	C	1533	1140	2207	861	1849	1384	502	1384
		R	3	2	95	25	18	45	46	25 *
%		C/R	0.196	0.175	4.30	2.90	0.973	3.25	9.16	2.90
Clozapine	40	C	1546	1267	1841	997	1156	928	607	1156
		R	0	0	0	57	0	0	0	0 *
%		C/R	0	0	0	5.72	0	0	0	0
+ Amphetamine	0.63	C	1598	1193	944	669	1240	1416	583	1193
		R	1592	195	951	148	42	319	465	319 * ⊛
%		C/R	99.6	16.3	101	22.1	3.39	22 5	79.8	22.5
Thioridazine	40	C	726	1062	1550	1255	2095	1164	658	1164
		R	32	525	43	19	247	9	271	43 *
%		C/R	4.41	49.4	2.77	1.51	11.8	0.773	41.2	4.41
+ Amphetamine	0.63	C	1231	996	909	584	1503	1435	510	996
		R	1360	1053	362	940	1441	1360	936	1053 ⊛
%		C/R	110	106	39 8	161	95.9	94 8	184	106
Chlorpromazine	40	C	1470	1501	2612	645	1613	1443	598	1470
		R	26	0	33	1	90	104	3	26 *
%		C/R	1.77	0	1.26	0.155	5.58	7.21	0.502	1.26
+ Amphetamine	0.63	C	1176	943	963	1301	1332	1219	610	1176
		R	1549	924	871	720	1374	1856	551	924 ⊛
%		C/R	132	98.0	90.4	55.3	103	152	90.3	98.0

* Significant difference ($p < .05$) between control- and drug session.

⊛ Significant difference ($P < .05$) between neuroleptic-treatment and combined neuroleptic-amphetamine treatment.

Wilcoxon matched-pairs signed-ranks test, two-tailed probability.

Table 10c: *Self-stimulation responses of individual rats, obtained during pre-drug control session (C) and after administration of either pimozide (0.63 mg/kg), 2 hrs before the session, or chlorpromazine (2.5 mg/kg), thioridazine (40 mg/kg), pipamperone or clozapine (40 mg/kg), 1 hr before the session, or these compounds followed by nomifensine (2.5 mg/kg), 1/2 hr before the session. All compounds were given subcutaneously, except for clozapine which was given orally.*

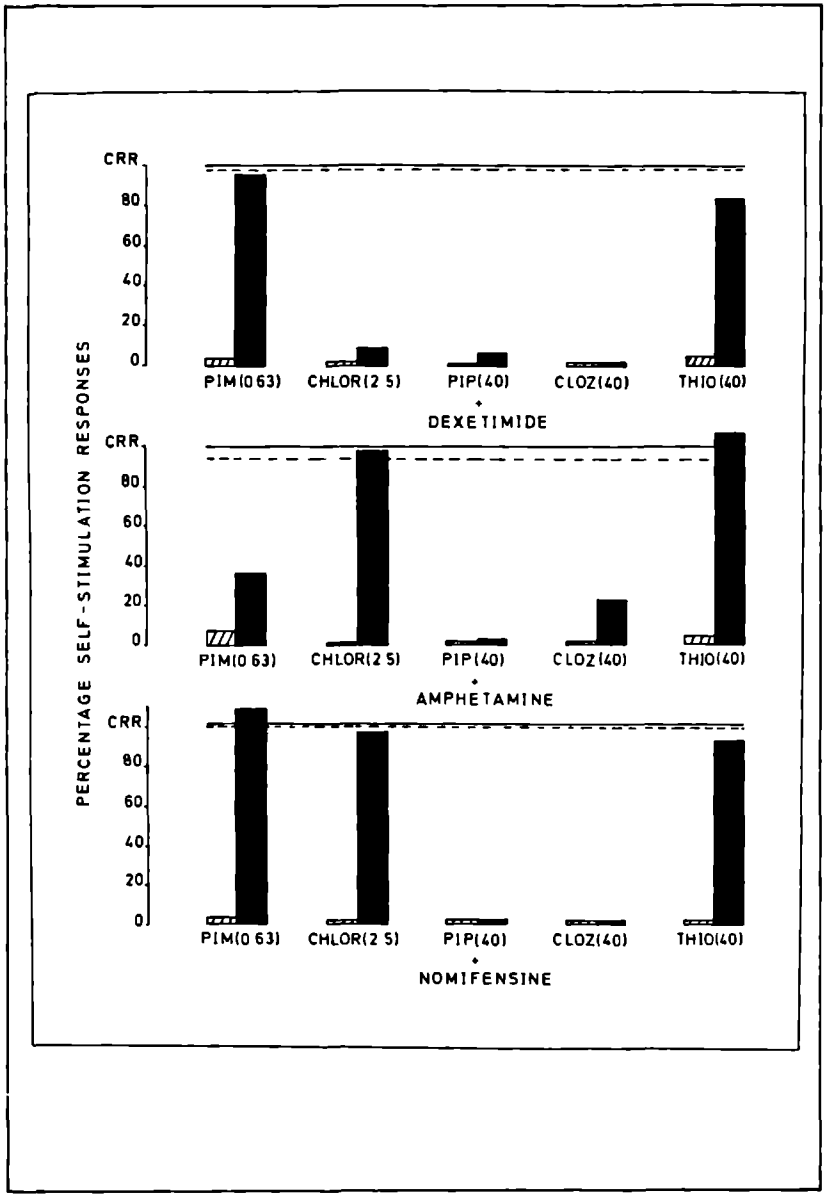
Self-stimulation responses/30 min										
Compound	Dose mg/kg		Rat # 1	2	3	4	5	6	7	Median
Control		C_1	1601	1386	2528	857	1749	1141	1942	1601
		C_2	1710	1236	2645	641	1667	1133	1929	1667
%		C_1/C_2	107.	89.2	105.	74.8	95 3	99 3	99.3	99 3
Nomifensine	2.5	R	1691	2104	2798	784	1439	1131	1918	1691
%		R/C_2	98 9	170.	106.	122.	86 3	99.8	99 4	99.8
Pimozide	0.63	C	1564	1407	2677	660	1591	1330	1882	1564
		R	10	44	14	109	35	19	0	19 *
%		C/R	0.639	3.13	0.523	16 5	2.20	1.43	0	1.43
+ Nomifensine	2.5	C	1617	1484	2530	381	1578	1346	1843	1578
		R	1944	2166	2723	61	2146	1334	1085	1944 Ⓝ
%		C/R	120	146	108	16 0	136	99 1	58 9	108
Chlorpromazine	2.5	C	1472	1255		733	1552	1340	1885	1406
		R	26	33		10	19	31	102	28 5 *
%		C/R	1.77	2.63		1 36	1 22	2.31	5 41	2 04
+ Nomifensine	2.5	C	1526	1226		924	1655	1401	1839	1463.5
		R	1748	948		776	1828	1571	549	1259 5 Ⓝ
%		C/R	115.	77.3		84 0	110	112	22 9	97
Thioridazine	40	C	1707	1359		555	1659	1491	1876	1575
		R	32	0		4	76	42	16	24 *
%		C/R	1.87	0		0.721	4.58	2.82	0 853	1 36
+ Nomifensine	2.5	C	1489	1683		881	1716	912	1891	1586
		R	1708	1383		956	1554	857	834	1169.5 Ⓝ
%		C/R	115.	82 2		109.	90 6	94 0	44.1	92.3
Pipamperone	40	C	1378	1431		579	1829	1521	1493	1462
		R	0	13		0	56	28	7	10 *
%		C/R	0	0.908		0	3.06	1 84	0.469	0.6885
+ Nomifensine	2.5	C	1264	1179		795	1608	1133	1516	1221.5
		R	0	28		0	0	65	0	0 *
%		C/R	0	2.4		0	0	5 7	0	0
Clozapine	40	C	1198	846		620	1621	618	1601	1022
		R	0	0		9	10	0	59	4 5 *
%		C/R	0	0		1 45	0 617	0	3 69	0.3085
+ Nomifensine	2.5	C	1100	1327		779	1771	661	1853	1213 5
		R	0	75		0	0	0	96	0 *
%		C/R	0	5 7		0	0	0	5 2	0

* Significant difference ($p < .05$) between control- and drug session.

Ⓝ Significant difference ($p < .05$) between neuroleptic-treatment and combined neuroleptic-nomifensine treatment.

Wilcoxon matched-pairs signed-ranks test, two-tailed probability.

Fig. 13: Self-stimulation in rats: median (7 rats) response rate expressed as a percentage of the preceding control (= 100 %) obtained after the neuroleptics (▨) pimozide (PIM), chlorpromazine (CHLOR), pipamperone (PIP), clozapine (CLOZ) and thioridazine (THIO) and combined (■) neuroleptic treatment with dexetimide, amphetamine and nomifensine.



Finally, the thioridazine-induced inhibition was equally antagonized to control levels with dexetimide, amphetamine and nomifensine.

7.4. General discussion

Dexetimide is considered to have reversed the specific neuroleptics because of its indirect action on DA, while amphetamine could reverse some neuroleptic effects, because of its releasing properties of DA and NA. According to the classification described in section 6 chlorpromazine and possibly also pipamperone, belong to the category of neuroleptics which are characterized by a low ratio of DA- to NA-receptor blocking activity (see also Andén et al., 1970).

The results of the drug-antagonistic studies here, indicate that the presence or lack of antagonistic effects depends on the relative potency of the NA- versus DA-blocking activity achieved with the neuroleptics, but cannot be exclusively based on this ratio. Snyder et al. (1974) proposed that neuroleptics exerting antipsychotic activity but seemingly inducing fewer extrapyramidal effects, are compounds with inherent anticholinergic activity. One would expect anticholinergics to further enhance the anticholinergic activity and, thus, to completely antagonize the DA-blocking effect. This would explain why dexetimide quite effectively reversed the thioridazine-induced inhibition. However, the latter effect cannot be solely explained by a relatively high antagonistic potency at muscarinic receptor sites (Iversen, 1975), since clozapine was even more potent but was not reversed in our experiments. If the thioridazine NA-blocking effect is a more peripheral phenomenon, it could be assumed that the DA-blocking effect of thioridazine is responsible for the self-stimulation inhibition. Consequently, the inhibition could be antagonized with anticholinergics as well as with DA-uptake blocking drugs. With the tests available central, as well as peripheral NA effects, are probably being measured. The two effects have not yet been separated. Further experiments are required to indicate whether a peripheral or a central NA receptor blocking activity is involved.

The neuroleptic-antagonistic effect obviously does not depend on simple mechanisms. The results reported evidenced that anticholinergic as well as DA-uptake blocking activity are able to overcome the inhibition.

DA-agonists have been used with variable success in the treatment of parkinsonism: both apomorphine (Cotzias et al., 1970, 1972) and piribedil (Sweet et al., 1974; Vakil et al., 1973) affected tremor and rigidity. These two direct receptor stimulating agents were not able to antagonize the neuroleptic-induced self-stimulation inhibition. These results point to the difference between the receptor blocking activity and parkinsonism, the latter being due to a degeneration of the nigrostriatal DA pathway (Hornykiewicz, 1971) resulting in a lack of DA input to the striatum and a distorted balance between the transmitters operating in the caudate (Cools et al., 1975). One should not forget, however, that the action of apomorphine is far more complex than was originally supposed (Costall and Naylor, 1973 and see survey Colpaert et al., 1976c).

Desipramine, which is claimed to exert its antidepressant activity by blocking the uptake of NA, did not antagonize the pimozide-induced inhibition.
Desipramine, at the doses used, also possesses α-adrenergic blocking activity which could further potentiate the inhibition (see chapter VI, section 3.6). It is interesting to note that dexamisole was able to antagonize the pimozide-induced inhibition. Dexamisole is, however, devoid of anticholinergic blocking activity (Van Nueten, 1972), but is described as having amine-blocking effects (Vanhoutte and Van Nueten, 1975). The failure of this compound to cause antagonism in all rats probably reflects its less specific effects on DA.
The results with nomifensine clearly indicate that the anticholinergic activity, in itself, is not a prerequisite for antagonism of specific DA inhibition. It is not known whether such a direct mechanism could also account, at least partially, for the dexetimide-reversal properties. This has to be elucidated by further biochemical studies. The antagonism of the neuroleptic self-stimulation inhibition may be more specific for DA-uptake blockers than with the anticholinergics. As mentioned (see 7.1.), relatively high doses of the anticholinergics are required.
The results of the interaction of pimozide with various antagonists favour the supposed connection between DA and ACh neurons. The interaction could be explained by an interference at the level of the inhibitory DA neurons. It has indeed been suggested that there may be 2 different types of DA neurons, the second being excitatory and operating in the same way as the cholinergic striatal neurons (Cools, 1973).
Neuroleptic treatment increased homovanillic acid (HVA) content in the striatum and in the limbic structures, an effect suggesting an increased DA turnover. Neuroleptics also increase the release of ACh and decrease its content in the striatum (Guyenet et al., 1975; McGeer et al., 1974; Stadler et al., 1973) but not in the limbic system (Andén, 1972; Bartholini et al., 1973; Lloyd et al., 1973) or other brain structures, such as the cortex and the hippocampus (Sethy and Van Woert, 1973). Furthermore, in the striatum but not in other brain structures, the neuroleptic-induced increase of HVA content is effectively antagonized by anticholinergics (Consolo et al., 1974; Stadler et al., 1973), whereas cholinergic drugs have been found to increase striatal HVA concentrations (Andén, 1974). Since complete antagonism of a DA-blocker with an anticholinergic is possible, the reported data might indicate that the inhibition of self-stimulation is mainly due to an interference with DA sites in striatum.

8. CONCLUSIONS

A variety of neuroleptics belonging to various chemical classes and with widely different pharmacological profiles were tested on brain self-stimulation. The neuroleptics were differentiated according to the effects obtained in pharmacological tests and on the basis of drug-interaction studies. The characteristics of the neuroleptic effects were described and will be discussed in the following section with the aim of formulating a

hypothesis on the impairment of self-stimulation and of operant behaviour in general (8.1.). Further, some clinical implications will be described (8.2.).

8.1. Impairment of self-stimulation

The neuroleptics described here inhibited self-stimulation in a dose-dependent manner. They could be ranked according to a quantitative criterion, namely the ED_{50}-values of response inhibition from the most potent compound fluspiperone, to the least potent thioridazine.
The self-stimulation inhibition could be interpreted in terms of an impact on the response required to obtain the reward or in terms of an alteration of the motivation. Neither of these is sufficient to explain the described experiments. An alternative interpretation is that neuroleptics interfere with the sensorimotor integrative function subserved by the basal ganglia.

1. The fact that many types of behaviour are inhibited by neuroleptics might lead to the concept that the inhibition is due to an effect on motor performance. Effects on the motor function are to some degree causally related to the inhibition. The latter is suggested by the significant correlation found between self-stimulation inhibition and catalepsy. Further, the self-stimulation test is positioned between the catalepsy test and amphetamine-antagonism test (see 6.2.).
There are a number of observations suggesting that the ability to perform is still present in neuroleptic-treated rats: they start pressing the lever when placed in the self-stimulation cage; they self-stimulate for high SPC's, whilst low base-line levels are inhibited; finally, they press the lever, but licking for the same brain-stimulation is inhibited. High doses of neuroleptics cause motor deficits (catalepsy or sedation) which might be related causally to the self-stimulation inhibition. However, the inhibition cannot be explained solely by an effect on performance ability.

2. Self-stimulation inhibition could be explained in terms of a motivational deficit. However, the conditional motivation or anticipation of reward is not affected and the inhibition is, in contrast, independent of the motivational state.
Firstly, the cues associated with reinforcing brain-stimulation, conditional motivation (Trowill, 1976) are unaffected. Neuroleptic-treated rats tend to lever-press during the first minutes of the self-stimulation session at equal or higher rates than control animals. Thereafter, though, responding declines. In fact the response curves very much resemble extinction curves.
Secondly, the neuroleptic-induced inhibition of operant behaviour is independent of the nature of the motivational state. The performance of conditioned behaviour, whether the reinforcer is negative or positive, is equally well inhibited by neuroleptics. Therefore, it cannot be stated that neuroleptics specifically or exclusively alter the reward.
Thirdly, the differential inhibition of different base-line rates of respond-

ing can evidently not be related to drug-response effects. Inhibition is more easily obtained when behaviour operates at a low motivational level and vice versa. The differential effects could be interpreted in terms of an incentive model (Bolles, 1967) of brain self-stimulation (Gallistel, 1964; Trowill et al., 1969). Incentive motivation is conceived as a «response energized by anticipation of a stimulus and reinforced by its realization» (Seward et al., 1959, p. 294). According to this model, extinction and reinforcement are function of the characteristics of reward. Shifts from high to low reward cause negative contrast effects, shifts from low reward to high reward, cause positive contrast effects (Panksepp and Trowill, 1969, 1970).
In the experimental design we used (different SPC's given in a randomized order) high SPC's are more rewarding than the low SPC's. In the former case, the learned expectancy of reward is higher and habit strength stronger, because there has been more training (Trowill et al., 1969). Therefore, high SPC's could be more resistant to drug-effects. At low SPC's, frustration of non-reward is less and extinction is readily established.
Finally, neuroleptics could affect the perception of the reward consequences. There is no evidence, however, that they interfere with the perception of the reward itself but rather with the association between a response and its consequence.

3. It is alternatively emphasized that neuroleptics interfere at the level of sensorimotor integration. During the same experimental session licking for brain-stimulation was more inhibited than lever-pressing for the same reward. The difference in performance, determined by physiological characteristics of the response and partially by the different schedule applied, cannot account for the differential influence. Rats which made more lick responses were inhibited at lower doses than rats which performed at lower rates. Therefore, the difference in brain-stimulations received similarly fails to explain the differential influence. If neuroleptics inhibit self-stimulation by interfering with reward or the motor system, one would expect an equal inhibition regardless of the operant. The reward in both cases is the same; rats can apparently no longer associate the response and its consequence.

4. There are a number of behavioural studies, pharmacological experiments and lesioning experiments implicating the dopaminergic nigrostriatal system as a substrate of a stimulus-response association (see also Grossman, 1976). The dopaminergic nigrostriatal system is an indispensable link sustaining complex learned behaviour. This system is linked with the extrapyramidal structures which subserve integrative functions. The terminal structure, the caudate nucleus «forms a part of a system in which incoming signals are compared with previously established target values, i.e. links between two or more responses forming an integrated sequence of elements ...» (Cools, 1973, p. 138). It is conceivable that the interference with these structures by neuroleptics is causally related to the inhibition.

It was shown in various experiments that aphagia and adipsia, earlier considered as a typical lateral hypothalamic syndrome (e.g. Anand and Brobeck, 1951; Teitelbaum and Epstein, 1962), were due to lesions of the nigrostriatal system (cell bodies or axons) (e.g. Ungerstedt, 1971b). In an experiment by Antelman and Szechtman (1975), tail-pinching was used to induce stimulus-bound behaviour. The particular response appeared to be determined by the stimulus-objects present in the environment (Valenstein, 1971). They described that consummatory behaviour was critically dependent on the dopaminergic nigrostriatal system.

Lesioning of the nigrostriatal system not only caused deficits in consummatory responses, but resulted in a complex behavioural syndrome (Grossman, 1970; Grossman and Grossman, 1971). The impairment of learned behaviour (Kent and Grossman, 1973) depends on the extent of the transsections of fibres. Recovery and relearning occurred when lesions were smaller. With large lesions, reacquisition of lever-pressing for brain-stimulation proved impossible. Learning deficits were also shown after intraventricular injection of 6-hydroxy-dopamine (Mason and Iversen, 1974). However, it was not clear whether the depletion of dopamine or of noradrenaline was responsible for the observed effects. Acquisition and performance in positively or negatively reinforced situations are seriously affected by lesions of the substantia nigra, the nigrostriatal pathway and the caudate nucleus (e.g. Kirkby, 1970). See Cools (1973) for a survey on the literature implicating the caudate nucleus in highly complex behavioural performances.

Electrical stimulation of the substantia nigra (Routtenberg and Holzman, 1973), or lesioning of the caudate nucleus (Mikulas and Isaacson, 1965) also disrupted retention, which showed these structures to be involved in processed inputs. Routtenberg and Holzman (1973) suggested that the substantia nigra (zona compacta) might be physiologically active during learning.

All these points suggest that the dopaminergic nigrostriatal system is highly involved in integrative processes during acquisition, learning, retention and performance of complex operant behaviour. In other words this system appears to be critically involved in the organisms' responsiveness to environmental stimuli (Antelman and Szechteman, 1975; Zigmond and Stricker, 1973).

The experiments of Huston and Borbély (1973) and Huston and Ornstein (1976) clearly demonstrated that the dopaminergic nigrostriatal system is not critically involved in less complex behaviour. Learning in the thalamic preparation (i.e. rats with extensive lesions of the cortex hippocampus, septem and striatum) is, however, not adaptive since the response failed to become extinguished.

Neuroleptics inhibit self-stimulation as well as other operant behaviours by virtue of the effect on the stimulus-response association. The degree to which this occurs depends on the complexity of the response and the complexity of the association. The substrate on which neuroleptics impinge is the dopaminergic nigrostriatal system. The latter system is linked up to a reinforcing-reward substrate underlying complex behaviour

and forms a part of the structures subserving a sensorimotor integrative function.

8.2. Clinical implications

Experimental studies on the interaction of neuroleptics with other drugs are few. One of the reasons for this could be the difficulty in obtaining reliable and quantitative data. There is, however, an obvious need for such studies. Firstly, neuroleptic-induced parkinsonian-like effects could be of heuristic value for a better understanding of the treatment of parkinsonism. The drawback related to this model is the different aetiology: parkinsonism is mainly related to a degeneration of dopaminergic neurons, while the neuroleptic-induced effects are due to a postsynaptic receptor blockade.
Secondly, psychotics are routinely given antiparkinsonian drugs in conjunction with neuroleptics, in order to alleviate extrapyramidal side-effects (associated with high doses of neuroleptics).
The self-stimulation inhibition and its antagonism or reversal showed that self-stimulation was a reliable tool providing quantitative data.
Drugs effective in the treatment of parkinsonism reversed the self-stimulation inhibition. It was shown that anticholinergic activity was not a prerequisite, but that drugs which block dopamine-uptake were also potent antagonists. Apomorphine, as well as piribedil, were ineffective as antagonists. Yet, both compounds have been used in the treatment of parkinsonism. Nomifensine, according to Costall et al. (1975), resembles apomorphine in that its stereotypic action was still present after disruption of presynaptic events. It was concluded that nomifensine could be used as a potential antiparkinsonian agent (preliminary clinical data confirmed this action, B. Costall, pers. communication). The antagonism of the neuroleptic-induced inhibition is not dependent upon its direct receptor activating properties. Rather, it is the ability of nomifensine to inhibit reuptake processes (Hunt et al., 1974) which accounts for its reversal properties.
If self-stimulation inhibition reflects more the neuroleptic effect and not the neurological deficit caused by neuroleptics, one would expect the antagonists effectively reversing the inhibition to reverse therapeutic effects, too. This action is assumed to be localized at the level of the extrapyramidal structures. It was found that L-dopa treatment of parkinson-patients elicited psychotic side-effects (Goodwin, 1971), and L-dopa-treated schizophrenics were made worse without improvement of the extrapyramidal side-effects (Yaruyura-Tobias et al., 1970). Similarly, treatment with DA-receptor stimulants such as piribedil, caused a deterioration of psychiatric status (Angrist et al., 1975).
Some clinical reports describe that antiparkinsonian drugs given in conjunction with neuroleptics induce a therapeutic reversal (Haase, 1972; Haase and Janssen, 1965; Singh and DiScipio, 1972; Singh and Kay, 1974, 1975; Singh and Smith, 1973a, b). Singh and Kay (1975) found that the counter-therapeutic effects were more extensive than originally

described (Singh and Smith, 1973). The counter-therapeutic reversal of the fundamental psychotic symptoms, was not due to some kind of toxic effect, but to an exacerbation of the disorder.
Singh and Kay (1975) speculated that the counter-therapeutic effects are due to an interference with a periventricular cholinergic system, reciprocally interacting with the facilitatory catecholaminergic system, in limbic forebrain structures described by Stein (1968).
It is conceivable that anticholinergic drugs influence striatal, limbic and cortical structures because in all these structures, cholinesterase and acetylcholinesterase are present (Lewis and Shute, 1967; Shute and Lewis, 1967). This influence is of particular relevance when it can be shown that in these structures monoaminergic-containing systems produce effects contrary to those of the cholinergic system (Shute and Lewis, 1967).
Many biochemical experiments substantiate the dopaminergic-cholinergic link in the caudate nucleus. Such a direct interaction in the limbic structures was, however, not evidenced (described in chapter 5). An interaction at the origin of the dopaminergic systems is not excluded and remains, therefore, a subject for further experimentation. Undoubtedly, anticholinergics influence the cholinergic neurons bypassing the dopaminergic links, whilst neuroleptics could affect dopamine functions in limbic structures, striatum and cortex. The different psychotic symptoms are probably also related to a dysfunctioning of various brain structures, which is at variance with the hypothesis of Snyder et al. (1974) that dopaminergic receptors of the mesolimbic system are the exclusive site for antipsychotic activity. Stevens (1973) pointed to the striking parallellism between the «limbic striatum» and the neostriatum. Dopaminergic cell bodies located in the ventral midbrain project to the neostriatum and the limbic striatum and further respectively to the globus pallidus and the substantia inominata. Further, the cortex topographically projects into the caudate-putamen on the one hand and the limbic striatum on the other hand (Kemp and Powell, 1970). Both the neostriatum and the limbic striatum could act as central gating mechanisms for cortical output. It is thus quite feasible that both structures, when pathologically functioning, are substrates of psychosis. Stevens (1973, p. 187) wrote that «Although the circumstantial evidence for abnormal function in a limbic striatal gate in schizophrenia is heuristically attractive, direct anatomical evidence is sparse.» Anatomical evidence for an abnormal striatum was, however, already described in 1955 by Mettler. The self-stimulation inhibition and its reversal probably reflects a part of the extensive counter-therapeutic effects found in the clinic. A failure of the cholinergic system in the striatum may be related to the social avoidance aspects described by Singh and Kay (1975).
The practical consequence is that one should avoid the routine use of antiparkinsonian drugs together with neuroleptics. Because high doses of specific neuroleptics cause extrapyramidal side-effects, the degree of parkinsonism has been used as an index of efficacy. The fact that both phenomena are related to a striatal dopaminergic receptor blockade leads to this erroneous conclusion and was experimentally contradicted by Bishop et al. (1965).

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Summary

The aim of this thesis was to study the influence of psychopharmacological substances on self-stimulation behaviour in rats (and dogs).

Chapter I introduces this study with a short historical description of the discovery of self-stimulation behaviour. The rewarding properties of electrical brain stimulation have been demonstrated in many species, including man and formed, together with the description of brain-structures in which electrical stimulation elicited aversive behavioural reactions, a new approach to a hedonistic description of behaviour. The self-stimulation system is assumed to be the substrate of appetitive behaviour. The description of neurotransmitters mediating the self-stimulation system has generated the catecholamine hypothesis. The pharmacological studies were then situated in a neurochemical frame.

Chapter II describes the aims of this study. These were, in short to provide a thorough quantitative analysis of the influence of psychoactive drugs, belonging to various pharmacological and chemical classes, on self-stimulation behaviour. The qualitative interpretation is related to the question of whether drugs affect self stimulation behaviour specifically (for example on the reinforcing process) or rather unspecifically (for example changing general activity level).

Chapter III gives a survey of the literature (period 1956, first publication, to 1974 + 1975) on the pharmacological influence of self-stimulation. Methods as well as results are described in tables. No comparative study has been made as this would be extremely difficult in view of the fact that the description of results is often inadequate and that there is a tremendous diversity in methodology.

Chapter IV describes the general methods (subjects, surgery and materials) applied in this study. In addition, some critical aspects such as the type of electrode and the type of electrical stimulation, are considered.

Chapter V. The interpretation of the effects of drugs is partly dependent on control values. This required a study of the electrical stimulation parameters, since these are some of the major factors determing the frequency of self-stimulation. One of the questions was whether the frequency of lever-pressing was determined by individual. parameters

(intensity, pulse frequency, etc.) or by the total electrical change contained in a stimulation. A significant, although poor correlation between total electrical charge and self-stimulation rate, was found; further, each parameter needed to exceed a threshold. Finally, it is possible to predict the frequency of self-stimulation at least within certain limits, by selecting a certain combination of stimulation parameters (SPC).

Chapter VI. In a quantitative approach to behaviour, drug-effects are described as facilitatory or inhibitory depending on whether they increase or decrease self-stimulation. Therefore, a method (VI.1) was applied in which different SPC's (based on Chapter V) were presented to the rats in a specific sequence during daily one hour experiments. This method made it possible to determine both increase and decrease of self-stimulation, in the same rat during the same experiment.
Because the frequency of lever-pressing is determined by various factors such as type of stimulator, SPC's and their sequence, subjects and time, an adequate analysis of the control values required an analysis of variance (VI.2.). The drugs effects had to be compared with the values for the preceding control session with the same rats, the same SPC's and *during the same week of experiment, since the factors SPC, time,* subjects and their interaction were found significant. These results further necessitated the use of a parameter-free test of significance.
This section (VI.3) describes the effects of 18 psychoactive drugs of which 3 to 6 doses were given to groups of 3 to 6 rats, namely: 3 CNS-stimulants (cocaine, amphetamine, apomorphine), 3 anticholinergics (dexetimide, benztropine, scopolamine), 3 minor tranquillizers (chlordiazepoxide, diazepam, nitrazepam), 3 narcotic analgesics (morphine, fentanyl, piritramide), 3 antidepressants (desipramine, amitriptyline, dexamisole) and 3 hypnosedatives (etomidate, methohexital, pentobarbital).
Most drugs cause an increase as well as a decrease of self-stimulation. The effects are, however, dependent on the dose, injection time, control values and subjects. The depression of self-stimulation, for example by high doses of narcotic analgesics or CNS-stimulants, is an unspecific effect. The mechanism causing inhibition depends, however, on the particular drug. Inhibition can for instance, be due to the induction of muscle rigidity or to causing a competition between stereotype behaviour and adapted behaviour.
The facilitation of self-stimulation might be due either to a sensitization of the self-stimulation substrate or to a reduction of threshold. Since this substrate is considered as a substrate of the «immediate reinforcement» of behaviour, it can be assumed that these effects are specific. Further, it appeared that the effects of different drugs could not be explained by a direct interference on the self-stimulation substrate, but rather by an interference on inhibitory systems (cholinergic and serotonergic) involved in the suppression of behaviour or induction of fear. In essence, a «balance-theory» is proposed.

Chapter VII describes a quantitative analysis of the influence of 20 neuroleptics, belonging to various chemical groups, tested according to the method described in Chapter VI. The object was to find out whether the inhibition of self-stimulation behaviour could be explained in terms of a blockade of the motor system or rather in terms of a motivational deficit. Because different neuroleptics are dopaminergic blocking agents, special attention has been given to the role of the nigrostriatal system.

All neuroleptics inhibit self-stimulation in a dose-related way, but differ from one another in terms of potency. The inhibition can hardly be explained as being caused by a motorial effect. Further, it appeared that strongly motivated behaviour is less susceptible to inhibition than weakly motivated behaviour.

The response pattern seen after the administration of high doses of neuroleptics occurs in a way similar to that seen after applying an «extinction-procedure» (the elimination of the stimulation). The conditioned anticipation appears to be present, but the lack of sustained responding points to a diminution or even an elimination of the reinforcing value of the electrical stimulation. This could be caused by an increase of the threshold or by changing the motivational value of the stimulation.

In one of the experiments it appeared that another instrumental response used (in this case licking for stimulation) was more sensitive to the neuroleptic inhibition. This could mean that the complexity of the relation between response and stimulation is an important factor in the evaluation of the effects of a drug.

Little is known about the influence of neuroleptics on self-stimulation behaviour in other species. In the dog, it appears that neuroleptics, which preferentially interfere with noradrenergic systems, are potent inhibitors even of self-stimulation obtained in dopaminergic structures. This could indicate an interaction between noradrenergic and dopaminergic systems.

The classification of neuroleptics and their relation to pharmacological tests and behavioural tests was studied by a new method («spectral mapping»). The inhibition of self-stimulation caused by neuroleptics appeared to be more closely related to an interference on dopaminergic systems than to noradrenergic systems.

The inhibition of self-stimulation caused by specific neuroleptics could be antagonized by anticholinergics and drugs which enhance dopaminergic activity in a «physiological way». In addition, a distinction between sedative and incisive neuroleptics could be based on drug-interaction studies. Further, there are a number of possible clinical implications.

The dopaminergic nigrostriatal system appears, apart from being a substrate of self-stimulation, to be critically involved in the responsiveness of the organism towards environmental stimuli and is incorporated at the end of processes which lead to overt behaviour.

Samenvatting

Het doel van deze studie was na te gaan welke de invloed was van psychofarmaca op het zelfstimulatiegedrag van ratten (en honden).

Hoofdstuk I leidt de studie in met een korte historische beschrijving van de ontdekking van het zelfstimulatiegedrag. De belonende waarde van elektrische hersenstimulatie werd in verschillende species, ook de mens, aangetoond en vormde tesamen met de beschrijving van hersenstrukturen waarin elektrische stimulatie aversieve gedragsreakties uitlokte, een vernieuwde aanzet tot een hedonistische beschrijving van het gedrag.
Het zelfstimulatiesysteem zou het substraat van appetitief gedrag zijn. De beschrijving van de transmitters die het zelfstimulatiesysteem mediëren, heeft aanleiding gegeven tot de «catecholamine-hypothese». Meteen werden de farmakologische studies in een neurochemisch kader gesitueerd.

Hoofdstuk II omschrijft de doelstellingen van deze studie. Kort samengevat was het de bedoeling een grondige kwantitatieve analyze te maken van de invloed van psychofarmaca, behorende tot verschillende farmakologische en chemische klassen, op het zelfstimulatiegedrag.
De kwalitatieve interpretatie heeft betrekking op de vraag of de stoffen op specifieke (b.v. op het versterkingsproces) dan wel een onspecifieke wijze (b.v. verandering van algemeen aktiviteitsniveau) het zelfstimulatiegedrag beïnvloeden.

Hoofdstuk III geeft een zo volledig mogelijk overzicht van literatuurgegevens (periode 1956, eerste publikatie, tot 1974-1975) i.v.m. de farmakologische beïnvloeding van zelfstimulatie. Zowel methoden als resultaten werden getabelleerd. Een vergelijkende studie is niet voorhanden en uitermate moeilijk omwille van soms gebrekkige resultatenbeschrijving en de methodologische diversiteit.

Hoofdstuk IV beschrijft de algemene methodiek (subjecten, implantatie en materiaal) van het onderzoek. Daarbij worden enkele kritische aspecten, zoals het type elektrode en het type elektrische stimulatie behandeld.

Hoofdstuk V: Het beoordelen van de effekten van farmaca is gedeeltelijk afhankelijk van de kontrolewaarden. Dit vereist een studie van de

elektrische parameters van de stimulatie, gezien deze tot de determinerende faktoren voor de frekwentie van zelfstimulatie behoren. Eén van de vragen was of de individuele parameters (intensiteit, frekwentie van de pulsen, etc.) of, daarentegen, de totale elektrische lading bevat in de elektrische stimulatie, de frekwentie van het hefboomdrukken bepalen. Er werd een significante, doch lage correlatie gevonden tussen de totale elektrische lading en de frekwentie zelfstimulatie; verder diende iedere afzonderlijke parameter een drempelwaarde te overschrijden. Door de keuze van een bepaalde kombinatie van stimulatie-parameters (SPC) is het mogelijk de frekwentie van de zelfstimulatie althans binnen bepaalde grenzen, te voorspellen.

Hoofdstuk VI. In een kwantitatieve benadering van het gedrag, worden de effekten van farmaca als faciliterend of inhiberend beschreven, naargelang ze de frequentie van zelfstimulatie verhogen of verlagen. Daartoe werd een methode (VI.1.) gebruikt waarbij verschillende SPC's (gebaseerd op hoofdstuk V) in een bepaalde volgorde aan ratten gepresenteerd werden gedurende dagelijkse experimenten van één uur. Deze methode liet toe zowel stijging als daling van de zelfstimulatie vast te stellen bij eenzelfde rat tijdens eenzelfde experiment.
Gezien de frekwentie hefboomdrukken bepaald wordt door verschillende faktoren zoals type stimulator, SPC's en hun volgorde, subjecten en tijd, vereiste een adekwate analyse van de kontrole resultaten een variantie-analyse (VI.2). Gezien de faktoren SPC, tijd en subjecten en hun interaktie significant bevonden werden, diende de analyse van de effekten van farmaca beschreven te worden in vergelijking met de voorafgaande kontrolesessie bij dezelfde ratten, dezelfde SPC's en gedurende dezelfde week. Verder impliceerde dit het gebruik van een parametervrije signifikatietoets.
In dit hoofdstuk (VI.3) worden de effekten van 18 psychofarmaca, waarvan 3 tot 6 dosissen aan groepen van 3 tot 6 ratten gegeven werden, beschreven: met name 3 CNS-stimulantia (cocaïne, amphetamine, apomorphine), 3 anticholinergica (dexetimide, benztropine, scopolamine), 3 minor tranquillizers (chlordiazepoxide, diazepam, nitrazepam), 3 narcotisch analgetica (morphine, fentanyl, piritramide), 3 antidepressiva (desipramine, amitriptyline, dexamisole), 3 hypnosedativa (etomidate, methohexital, pentobarbital). De meeste stoffen veroorzaken zowel een stijging als een daling van de zelfstimulatie. De effekten zijn evenwel afhankelijk van dosis, injectietijd, kontrolewaarden en subjecten.
De remming van de zelfstimulatie, veroorzaakt door bijvoorbeeld hoge doseringen van narcotisch analgetica of CNS-stimulantia, is een onspecifiek effekt. Het mechanisme waardoor de remming veroorzaakt wordt, verschilt echter naargelang de soort stof. Inhibitie kan te wijten zijn aan bij voorbeeld, het induceren van spierrigiditeit en verlies van oprichtingsreflex of, door een kompetitie van stereotiep gedrag met aangepast gedrag.
Facilitering van het zelfstimulatiegedrag kan o.m. te wijten zijn aan een sensitizering van het zelfstimulatiesubstraat of een verminderde drempelwaarde. Gezien dit substraat beschouwd wordt als het substraat voor de

«onmiddellijke versterking» van het gedrag, kan aangenomen worden dat dergelijke effekten specifiek zijn. Verder bleek dat de effekten van verschillende farmaca niet noodzakelijk te verklaren zijn vanuit een rechtstreeks aangrijpen op het zelfstimulatiesubstraat maar veeleer vanuit het aangrijpen op inhiberende systemen (cholinerge en serotonerge) betrokken in onderdrukking van het gedrag of het induceren van vrees. In essentie wordt een «balans»-theorie voorgestaan.

Hoofdstuk VII beschrijft een kwantitatieve analyse van de invloed van 20 neuroleptica behorende tot verscheiden chemische groepen, getest volgens dezelfde methode als beschreven in Hoofdstuk VI. De vraag werd gesteld of de inhibitie van het zelfstimulatiegedrag te verklaren is vanuit een motorische remming of veeleer vanuit een motivationeel deficiet. Omwille van het feit dat verschillende neuroleptica dopaminerg blokkerende stoffen zijn, werd vooral aandacht besteed aan de rol van het nigrostriataal systeem.
Alle neuroleptica remmen de zelfstimulatie op een dosis-gerelateerde wijze, maar verschillen in de eerste plaats van elkaar in termen van potentie. De inhibitie kan moeilijk alleen vanuit een motorisch effekt verklaard worden. Verder bleek dat sterk gemotiveerd gedrag moeilijker te onderdrukken valt dan zwak gemotiveerd gedrag.
Het antwoordpatroon na toediening van vrij hoge doseringen verloopt op een wijze gelijkaardig aan deze die men aantreft bij het toepassen van een «extinctieprocedure» (het uitschakelen van de stimulatie).
De gekonditioneerde anticipatie blijkt dus nog aanwezig te zijn, maar het gebrek aan doorzetting wijst op een vermindering op zelfs een uitschakeling van de versterkende waarde van de elektrische stimulatie. Dit zou kunnen het gevolg zijn van een drempelverhoging of door verandering van de motivationele waarde van de stimulatie.
In één van de experimenten bleek dat het gebruik van een andere instrumentele respons (in dit geval likken voor stimulatie), gevoeliger te zijn aan de neuroleptische onderdrukking. Dit zou erop kunnen wijzen dat de complexiteit van de relatie tussen respons en stimulatie een belangrijke faktor is in de evaluatie van de effekten van farmaca.
Weinig is bekend over de invloed van neuroleptica op het zelfstimulatiegedrag bij andere species. Bij de hond blijken neuroleptica die preferentieel op noradrenerge systemen inwerken, potente inhibitoren zelfs op zelfstimulatie verkregen in dopaminerge strukturen. Dit kan wijzen op een interaktie tussen noradrenerge en dopaminerge systemen.
De klassifikatie van de neuroleptica en de relatie tot farmakologische testen en gedragstesten werd met een nieuwe methode («spectral mapping») onderzocht. De inhibitie van zelfstimulatie door neuroleptica vertoonde een grotere relatie met de aangrijping op dopaminerge systemen dan op noradrenerge systemen.
De inhibitie van zelfstimulatie door specifieke neuroleptica kon antagoneerd worden door anticholinergica en stoffen die op een «fysiologische wijze» de dopaminerge aktiviteit verhogen. Tevens kon het onderscheid tussen sedatieve en incisieve neuroleptica op basis van interaktiestudies bepaald worden. Verder zijn er een aantal mogelijke klinische implicaties.

Het dopaminerg nigrostriataal systeem blijkt naast een substraat voor zelfstimulatie, kritisch betrokken te zijn in de responsiviteit van het organisme t.o.v. omgevingsstimuli en is ingeschakeld aan het einde van processen die leiden tot overt gedrag.

Curriculum vitae

Albert Wauquier werd geboren op 17 februari 1940 te Menen (België). Hij volgde acht studiejaren van de lagere school te Menen van 1945 tot 1953 en vervolgens de Lagere Normaalschool in het St.-Jozefsinstituut te Torhout, alwaar hij het diploma van onderwijzer en catechist in juli 1958 behaalde. Daarna volgde hij de Middelbare Normaalschool in het St.-Jozefsinstituut te Torhout en werd laureaat in de afdeling lichamelijke opvoeding in juli 1960. Tot 1965 was hij leraar lichamelijke opvoeding in verschillende onderwijstakken (lagere school, humaniora en normaalschool) in hetzelfde instituut. Van 1965 tot eind juni 1970 was hij fulltime leraar algemene vakken in het lager secundair technisch- en beroepsonderwijs in hetzelfde instituut. In oktober 1966 deed hij zijn aanvraag tot toelating aan de Rijksuniversiteit Gent en verkreeg die op 28 december 1966 (besluit van de Raad van Beheer, Rijksuniversiteit Gent op 7/12/1966).
In juli 1968 behaalde hij met onderscheiding het kandidaatsdiploma in de Pedagogische en Psychologische Wetenschappen. Tijdens de periode juli-augustus 1969 verrichtte hij experimenteel onderzoek in de researchafdeling van Janssen Pharmaceutica, i.v.m. de licenciaatsverhandeling over de farmacologische beïnvloeding van leren bij de rat. In juli 1970 behaalde hij met onderscheiding het licenciaatsdiploma in de Pedagogische en Psychologische Wetenschappen, richting ontwikkelings- en experimentele psychologie. Sinds september 1970 is hij verbonden als wetenschappelijk medewerker in de afdeling farmacologie van Janssen Pharmaceutica, waar hij werkzaam is in het domein van de experimentele psychofysiologie. In april 1975 organizeerde hij de «First international conference on Brain stimulation reward». Op basis van getuigschriften en bekomen studieresultaten werd hij op 28 augustus 1975 door het College van Decanen van de Katholieke Universiteit te Nijmegen als doctorandus aanvaard.
Het onderzoek in de voorbije jaren heeft geleid tot volgende lijst van publikaties:

List of publications

1. Wauquier, A.:
   Circadian rythm of brain self-stimulation in rats and resistance to long-term effects of psychopharmacological substances.
   J. interdiscipl. Cycle Res., 340-346 (1974)
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   Psychopharmacologia, **27**, 191-202 (1972)
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Stellingen

1. «Electrical stimulation produces little that resembles the normal» (Cobb, 1961) negeert de belangrijke vraag» ... how the application of a crude train of messageless electricity may result in the performance of highly refined and complicated response» (Delgado, 1969).
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3. Het corticale alpharitme vertoont een topografische relatie met, en wordt gereguleerd vanuit thalamuskernen. Het is echter weinig vruchtbaar dit fenomeen op basis van een deterministisch pacemaker concept uit te leggen.
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4. De methode gebruikt door de groep van S.H. Snyder om de distributie van enkephaline in het centraal zenuwstelsel te bestuderen kan gemakkelijk tot artefacten leiden.
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5. De opmerking «Find out about dreams and you will find out about insanity» (J.H. Jackson, 1911), moge fraai klinken doch brengt het probleem niet dichter bij een oplossing.
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6. De beweringen als zouden neuroleptica specifiek interageren met de opiate receptor zijn ongegrond.
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7. Een probabilistische psychologische leertheorie is te verkiezen boven een eclectische benaderingswijze.

8. Het operationeel definiëren van psychologische concepten leidt veelal tot een begripsdevaluatie.

9. Theoretische speculatie wordt soms meer geacht dan de feiten waarop een theorie steunt.
   L. Stein, C.D. Wise, Science **171**, 1032-1036 (1971)
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10. De laattijdige ontdekking van de REM-slaap fase is te wijten aan het feit dat descriptief werk nog veelal ten onrechte ondergeschikt wordt beschouwd aan experimenteel werk.
    W.C. Dement, M.M. Mitler, in: Basic mechanisms of sleep, O. Petre-Quadens, J.D. Schlag (Eds.), New York, Academic Press, 1974, pp. 271-296.

11. Het buiten beschouwing laten van experimentele resultaten op basis van hun lage significante waarde op het overschatten van resultaten die net significant bevonden werden, devalueert de statistische toetsing.

12. Het bijna obligaat invoeren van een scherts-stelling kan de oorzaak zijn van ongezellige denkverrichtingen.

A. Wauquier

Nijmegen, 8 oktober 1976